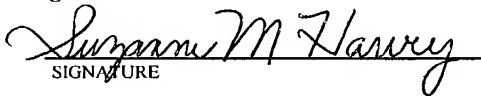


10/03/1999  
 RECEIVED  
 15 JAN 2002

FORM PTO-1390 (REV. 11-2000)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER A0000104-01-SMH
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371			U.S. APPLICATION NO. (If known, see 37 CFR 1.5) <b>10/031149</b>
INTERNATIONAL APPLICATION NO. PCT/US00/18346	INTERNATIONAL FILING DATE 5 July 2000	PRIORITY DATE CLAIMED July 16, 1999	
TITLE OF INVENTION Method for Treating Chronic Pain Using Mek Inhibitors			
APPLICANT(S) FOR DO/EO/US BARRETT, Stephen Douglas, BRIDGES, Alexander James, DIXON, Alistair, LEE, Kevin, PINNOCK, Robert Denham, TECLE, Haile, ZHANG, Lu-Yan			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
<p>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.</p> <p>4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <p>a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</p> <p>b. <input checked="" type="checkbox"/> has been communicated by the International Bureau.</p> <p>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</p> <p>6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).</p> <p>a. <input type="checkbox"/> is attached hereto.</p> <p>b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4).</p> <p>7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <p>a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</p> <p>b. <input type="checkbox"/> have been communicated by the International Bureau.</p> <p>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</p> <p>d. <input type="checkbox"/> have not been made and will not be made.</p> <p>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).</p> <p>9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p>			
Items 11 to 20 below concern document(s) or information included:			
<p>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input type="checkbox"/> A FIRST preliminary amendment.</p> <p>14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</p> <p>15. <input type="checkbox"/> A substitute specification.</p> <p>16. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.</p> <p>18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</p> <p>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</p> <p>20. <input checked="" type="checkbox"/> Other items or information:          International Search Report (PCT/ISA/210)          International Preliminary Examination Report (PCT/IPEA/409)          Certificate of Mailing by Express Mail</p>			

Express Mail No. EF378128657US  
 PD-A0000104-01-SMH

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)		INTERNATIONAL APPLICATION NO. PCT/US00/18346		ATTORNEY'S DOCKET NUMBER A0000104-01-SMH	
10/031149					
21. <input checked="" type="checkbox"/> The following fees are submitted: <b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. .... \$1000.00  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... \$860.00  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$710.00  International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$690.00 International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$100.00 <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				CALCULATIONS PTO USE ONLY	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	860.00
				\$	130.00
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	
Total claims	33 - 20 =	13	x \$18.00	\$	234.00
Independent claims	1 - 3 =		x \$80.00	\$	0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				\$	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$	1,224.00
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				\$	
<b>SUBTOTAL =</b>				\$	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
<b>TOTAL NATIONAL FEE =</b>				\$	1,224.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$	
<b>TOTAL FEES ENCLOSED =</b>				\$	1,224.00
				<b>Amount to be refunded:</b>	\$
				<b>charged:</b>	\$
a. <input type="checkbox"/> A check in the amount of \$ _____ to cover the above fees is enclosed. b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. <u>23-0455</u> in the amount of \$ <u>1,224.00</u> to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>23-0455</u> . A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. <b>WARNING:</b> Information on this form may become public. <b>Credit card          information should not be included on this form.</b> Provide credit card information and authorization on PTO-2038.					
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.</b>					
SEND ALL CORRESPONDENCE TO Suzanne M. Harvey Warner-Lambert Company Patent Department 2800 Plymouth Road Ann Arbor, Michigan 48105 Telephone: (734) 622-2658 Facsimile: (734) 622-1553			 SIGNATURE _____ Suzanne M. Harvey NAME _____ 42,640 REGISTRATION NUMBER		

## METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS

5

### BACKGROUND

The invention features a method for treating chronic pain using MEK inhibitors. Chronic pain includes neuropathic pain, and chronic inflammatory pain.

10

Abnormality anywhere in a nerve pathway disrupts nerve signals, which in turn are abnormally interpreted in the brain, causing neuropathic pain. Neuropathic pain may be, for example, a deep ache, a burning sensation, or hypersensitivity to touch. Diseases or conditions associated with neuropathic pain include, without limitation, diabetic neuropathy, causalgia, plexus avulsion, neuroma, vasculitis, crush injury, viral infections (e.g., herpes virus infection or HIV), constriction injury, tissue injury, nerve injury from the periphery to the central nervous system, limb amputation, hypothyroidism, uremia, chronic alcoholism, post-operative pain, arthritis, back pain, and vitamin deficiencies.

20

Infections such as herpes zoster (shingles) can cause nerve inflammation and produce postherpetic neuralgia, a chronic burning localized to the area of viral infection. Hyperalgesia is when an already noxious stimulus becomes more painful, and allodynia, when a previously non-noxious stimulus becomes painful (such as contact of clothing or a breeze). Reflex sympathetic dystrophy is accompanied by swelling and sweating or changes in local blood flow, tissue atrophy, or osteoporosis. Causalgia, including severe burning pain and swelling, sweating, and changes in blood flow, may follow an injury or disease of a major nerve such as the sciatic nerve. Some types of chronic low back pain can have a neuropathic component (e.g., sciatica, postpoliomyelitis and CPRM). Neuropathic pain may also be induced by cancer or chemotherapy.

30

Neuropathic pain is currently treated with anticonvulsants such as carbamazepine and antidepressants such as amitryptaline. NSAIDS and opioids generally have little effect (*Fields et al 1994 Textbook of Pain p 991-996 (pub: Churchill Livingstone), James & Page 1994*

5 *J.Am.Pediatr.Med.Assoc, 8: 439-447, Galer, 1995 Neurology 45 S17-S25.*

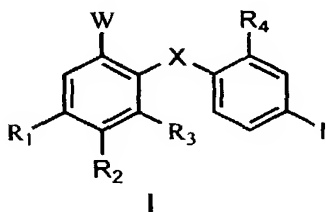
Neuropathic conditions that have been treated with gabapentin include: postherpetic neuralgia, postpoliomyelitis, CPRM, HIV-related neuropathy, trigeminal neuralgia, and reflex sympathetic dystrophy (RSD).

The generally weak efficacy of antiinflammatory agents suggests that the  
10 mechanism for chronic pain is separate from hyperalgesia.

### SUMMARY OF THE INVENTION

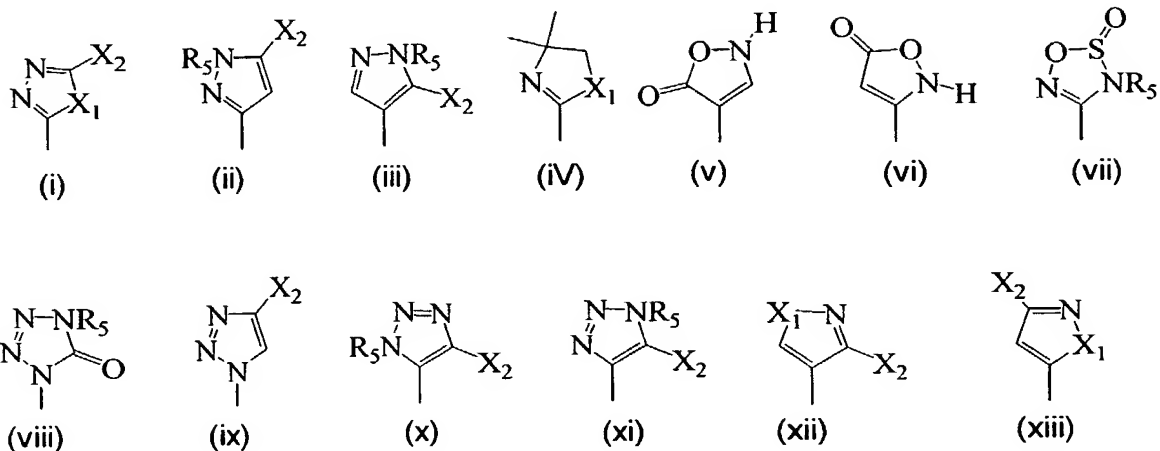
The invention features a method for treating chronic pain, which  
15 method includes the step of administering a composition including a MEK inhibitor to a patient in need of such treatment. Chronic pain includes neuropathic pain, idiopathic pain, and pain associated with vitamin deficiencies, uremia, hypothyroidism post-operative pain, arthritis, back pain, and chronic alcoholism. The invention also features compositions as  
20 disclosed, formulated for the treatment of chronic pain. Such a composition may include one or more MEK inhibitor compounds having a structure disclosed in patent application PCT/US99/30416, international filing date December 21, 1999.

Examples of MEK inhibitors include a compound having the formula (I)  
25 below:

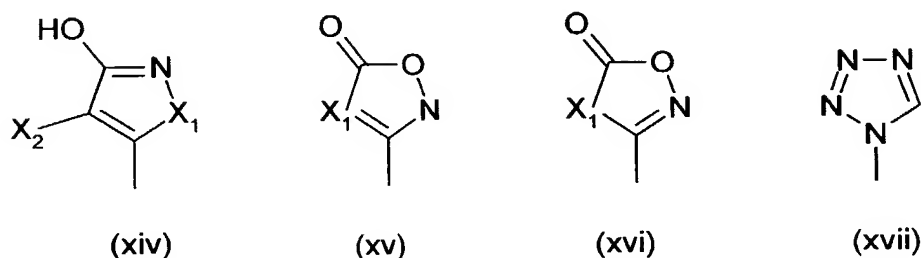




W is one of the following formulae (i) – (xiii):



5



10

$X_1$  is O, S, or  $NR_F$ .  $X_2$  is OH, SH, or  $NHR_E$ . Each of  $R_E$  and  $R_F$  is H or  $C_{1-4}$  alkyl; each of  $R_1$  and  $R_2$  is independently selected from H, F,  $NO_2$ , Br and Cl;  $R_1$  can also be  $SO_2NR_GR_H$ , or  $R_1$  and  $R_2$  together with the benzene ring to which they are attached constitute an indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole.  $R_3$  is selected from H and F; each of  $R_G$ ,  $R_H$ , and  $R_4$  is independently selected from H, Cl and  $CH_3$ .  $R_5$  is H or  $C_{1-4}$  alkyl. Each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and  $NO_2$ . Each heterocyclic radical

15

above is optionally substituted with between 1 and 3 substituents independently selected from halo, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-4</sub> alkenyl, C<sub>3-4</sub> alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO<sub>2</sub>, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 2 substituents independently selected from halo, C<sub>1-2</sub> alkyl, hydroxyl, amino, and NO<sub>2</sub>. The invention also features a pharmaceutically acceptable salt or C<sub>1-8</sub> ester of a disclosed compound. For example, the disclosed alcohol compounds may form esters having the structure obtained by replacing the H of a hydroxyl group with a -C(=O)C<sub>1-7</sub> acyl group.

Preferred embodiments of the invention include methods of using one or more of the following compounds:

- (a) said MEK inhibitor has a structure selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; (2,3-difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)-(4-iodo-2-methyl-phenyl)-amine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-ylamine; and 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; and
- (b) said MEK inhibitor has the structure selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid.

Other aspects of the invention are provided in the description, examples and claims below.

## BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a bar graph representing the paw withdrawal threshold (PWT) in grams as a function of time in days. The empty, cross-hatched, and single-

hatched bars are vehicle, PD 198306, and pregabalin, respectively. The arrows indicate time of drug administration (30 mg/kg, p.o.).

FIG 2. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single p.o. administration of PD 198306 (3-30mg/kg), or pregabalin (30mg/kg) and withdrawal thresholds were re-assessed 1h after treatment. Treatments were repeated twice a day for two days. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-8).

FIG. 3. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single p.o. administration of PD 198306 (3-30mg/kg), or pregabalin (30mg/kg) and withdrawal thresholds were re-assessed 1h after treatment. Treatments were repeated twice a day for two days. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*\*P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6).

FIG. 4. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD 198306 (1-30 $\mu$ g/10 $\mu$ l), or pregabalin (100 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*P<0.05, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-9).

FIG. 5. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days.

Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD 198306 (1-30 $\mu$ g/10 $\mu$ l), or pregabalin (100 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles.

5 \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=6-8).

FIG. 6 is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days .

10 Animals received a single intraplantar (i.pl.) administration of PD 198306 (3mg/100 $\mu$ l), or an intrathecal injection of PD 198306 (30 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed 1h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*\*P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6-9).

15

FIG. 7. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days.

Animals received a single intraplantar (i.pl.) administration of PD 198306 (3mg/100 $\mu$ l), or an intrathecal injection of PD 198306 (30 $\mu$ g/10 $\mu$ l) and  
20 withdrawal thresholds were re-assessed 1h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles. \*\*P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6).

FIG. 8 is a bar graph representing the force required in grams to elicit  
25 paw withdrawal using von Frey hair filaments. Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD219622, PD297447, PD 184352, or PD 254552 (30 $\mu$ g/10 $\mu$ l), or pregabalin (100 $\mu$ g/10 $\mu$ l) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median  $\pm$  1<sup>st</sup> and 3<sup>rd</sup> quartiles.  
30 \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-8).

# DETAILED DESCRIPTION

The compounds disclosed herein are pharmaceutically active, for example, they inhibit MEK. MEK enzymes are dual specificity kinases involved in, for example, immunomodulation, inflammation, and proliferative diseases such as cancer and restenosis.

Proliferative diseases are caused by a defect in the intracellular signaling system, or the signal transduction mechanism of certain proteins. Defects include a change either in the intrinsic activity or in the cellular concentration of one or more signaling proteins in the signaling cascade. The cell may produce a growth factor that binds to its own receptors, resulting in an autocrine loop, which continually stimulates proliferation. Mutations or overexpression of intracellular signaling proteins can lead to spurious mitogenic signals within the cell. Some of the most common mutations occur in genes encoding the protein known as Ras, a G-protein that is activated when bound to GTP, and inactivated when bound to GDP. The above-mentioned growth factor receptors, and many other mitogenic receptors, when activated, lead to Ras being converted from the GDP-bound state to the GTP-bound state. This signal is an absolute prerequisite for proliferation in most cell types. Defects in this signaling system, especially in the deactivation of the Ras-GTP complex, are common in cancers, and lead to the signaling cascade below Ras being chronically activated.

Activated Ras leads in turn to the activation of a cascade of serine/threonine kinases. One of the groups of kinases known to require an active Ras-GTP for its own activation is the Raf family. These in turn activate MEK (e.g., MEK<sub>1</sub> and MEK<sub>2</sub>) which then activates MAP kinase, ERK (ERK<sub>1</sub> and ERK<sub>2</sub>). Activation of MAP kinase by mitogens appears to be essential for proliferation; constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream Ras signaling, for example by use of a dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants. Although Ras is not itself a protein kinase, it participates in the activation of

Raf and other kinases, most likely through a phosphorylation mechanism. Once activated, Raf and other kinases phosphorylate MEK on two closely adjacent serine residues, S<sup>218</sup> and S<sup>222</sup> in the case of MEK-1, which are the prerequisite for activation of MEK as a kinase. MEK in turn phosphorylates  
5 MAP kinase on both a tyrosine, Y<sup>185</sup>, and a threonine residue, T<sup>183</sup>, separated by a single amino acid.

This double phosphorylation activates MAP kinase at least 100-fold. Activated MAP kinase can then catalyze the phosphorylation of a large number of proteins, including several transcription factors and other kinases.  
10 Many of these MAP kinase phosphorylations are mitogenically activating for the target protein, such as a kinase, a transcription factor, or another cellular protein. In addition to Raf-1 and MEKK, other kinases activate MEK, and MEK itself appears to be a signal integrating kinase. Current understanding is that MEK is highly specific for the phosphorylation of MAP kinase. In fact,  
15 no substrate for MEK other than the MAP kinase, ERK, has been demonstrated to date and MEK does not phosphorylate peptides based on the MAP kinase phosphorylation sequence, or even phosphorylate denatured MAP kinase. MEK also appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK  
20 may require a prior strong interaction between the two proteins. Both this requirement and the unusual specificity of MEK are suggestive that it may have enough difference in its mechanism of action to other protein kinases that selective inhibitors of MEK, possibly operating through allosteric mechanisms rather than through the usual blockade of the ATP binding site,  
25 may be found.

The effect of the MEK inhibitor PD 198306 has been investigated in two animal models of neuropathic pain by assessing static allodynia with von Frey hairs.

Oral administration of PD 198306 (3-30mg/kg) had no effect in the model  
30 of chronic constriction injury of the sciatic nerve (CCI). However, after repeated administration (3 doses over two days) it had a transient effect in the diabetic neuropathy model (streptozocin). This may be due to disorders of the blood-

brain barrier induced by the diabetic condition in these animals, thus allowing central action of the compound. Intrathecal administration of PD 198306 (1-30 $\mu$ g) dose-dependently blocked static allodynia in both the streptozocin and the CCI models of neuropathic pain, with minimum effective doses (MED) of 3 and 10 $\mu$ g respectively. The highest dose used (30 $\mu$ g) totally blocked the maintenance of static allodynia, for up to 1h. Intraplantar administration of PD 198306 (3mg/100 $\mu$ l) at a dose 100-fold higher than the dose shown to be effective intrathecally (30 $\mu$ g/10 $\mu$ l) had no effect on static allodynia in either of the neuropathic pain models. This finding confirms the lack of effect seen after systemic administration and suggests a central site of action for the compound.

From this study we can suggest the use of MEK inhibitors as potential new therapeutic tools for chronic pain. The study of potential side-effects, especially related to memory, of future brain-penetrant MEK inhibitors will indicate the therapeutic window for this novel class of compounds in the treatment of pain.

## A. Terms

Certain terms are defined below and by their usage throughout this disclosure.

Alkyl groups include aliphatic (i.e., hydrocarbyl or hydrocarbon radical structures containing hydrogen and carbon atoms) with a free valence. Alkyl groups are understood to include straight chain and branched structures. Examples include methyl, ethyl, propyl, isopropyl, butyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, 2,3-dimethylpropyl, hexyl, 2,3-dimethylhexyl, 1,1-dimethylpentyl, heptyl, and octyl. Cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

Alkyl groups can be substituted with 1, 2, 3 or more substituents which are independently selected from halo (fluoro, chloro, bromo, or iodo), hydroxy, amino, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, arylalkyloxy, heterocyclic radical, and (heterocyclic radical)oxy. Specific examples include fluoromethyl, hydroxyethyl, 2,3-dihydroxyethyl, (2- or 3-furanyl)methyl, cyclopropylmethyl, benzyloxyethyl, (3-pyridinyl)methyl, (2- or 3-furanyl)methyl, (2-thienyl)ethyl, hydroxypropyl, aminocyclohexyl, 2-dimethylaminobutyl, methoxymethyl, N-pyridinylethyl, diethylaminoethyl, and cyclobutylmethyl.

Alkenyl groups are analogous to alkyl groups, but have at least one double bond (two adjacent  $sp^2$  carbon atoms). Depending on the placement of a double bond and substituents, if any, the geometry of the double bond may be *entgegen* (E), or *zusammen* (Z), *cis*, or *trans*. Similarly, alkynyl groups have at least one triple bond (two adjacent  $sp$  carbon atoms). Unsaturated alkenyl or alkynyl groups may have one or more double or triple bonds, respectively, or a mixture thereof; like alkyl groups, unsaturated groups may be straight chain or branched, and they may be substituted as described both above for alkyl groups and throughout the disclosure by example.

Examples of alkenyls, alkynyls, and substituted forms include *cis*-2-butenyl, *trans*-2-butenyl, 3-butylnyl, 3-phenyl-2-propynyl, 3-(2'-fluorophenyl)-2-propynyl, 3-methyl(5-phenyl)-4-pentylnyl, 2-hydroxy-2-propynyl, 2-methyl-2-propynyl, 2-propenylnyl, 4-hydroxy-3-butylnyl, 3-(3-fluorophenyl)-2-propynyl, and 2-methyl-2-



propenyl. In formula (I), alkenyls and alkynyls can be C<sub>2-4</sub> or C<sub>2-8</sub>, for example, and are preferably C<sub>3-4</sub> or C<sub>3-8</sub>.

More general forms of substituted hydrocarbon radicals include hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, and corresponding forms for the prefixes amino-, halo- (e.g., fluoro-, chloro-, or bromo-), nitro-, alkyl-, phenyl-, cycloalkyl- and so on, or combinations of substituents. According to formula (I), therefore, substituted alkyls include hydroxyalkyl, aminoalkyl, nitroalkyl, haloalkyl, alkylalkyl (branched alkyls, such as methylpentyl), (cycloalkyl)alkyl, phenylalkyl, alkoxy, alkylaminoalkyl, dialkylaminoalkyl, arylalkyl, aryloxyalkyl, arylalkyloxyalkyl, (heterocyclic radical)alkyl, and (heterocyclic radical)oxyalkyl. R<sub>1</sub> thus includes hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminocycloalkyl, aminoaryl, alkylalkenyl, (alkylaryl)alkyl, (haloaryl)alkyl, (hydroxyaryl)alkynyl, and so forth. Similarly, R<sub>A</sub> includes hydroxyalkyl and aminoaryl, and R<sub>B</sub> includes hydroxyalkyl, aminoalkyl, and hydroxyalkyl(heterocyclic radical)alkyl.

Heterocyclic radicals, which include but are not limited to heteroaryls, include: furyl, oxazolyl, isoxazolyl, thiophenyl, thiazolyl, pyrrolyl, imidazolyl, 1,3,4-triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, indolyl, and their nonaromatic counterparts. Further examples of heterocyclic radicals include piperidyl, quinolyl, isothiazolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuryl, tetrahydropyrrolyl, pyrrolidinyl, octahydroindolyl, octahydrobenzothiofuranyl, and octahydrobenzofuranyl.

Selective MEK 1 or MEK 2 inhibitors are those compounds which inhibit the MEK 1 or MEK 2 enzymes, respectively, without substantially inhibiting other enzymes such as MKK3, PKC, Cdk2A, phosphorylase kinase, EGF, and PDGF receptor kinases, and C-src. In general, a selective MEK 1 or MEK 2 inhibitor has an IC<sub>50</sub> for MEK 1 or MEK 2 that is at least one-fiftieth (1/50) that of its IC<sub>50</sub> for one of the above-named other enzymes. Preferably, a selective inhibitor has an IC<sub>50</sub> that is at least 1/100, more preferably 1/500, and even more preferably 1/1000, 1/5000, or less than that of its IC<sub>50</sub> or one or more of the above-named enzymes.

## B. Compounds

One aspect of the invention features the disclosed compounds shown in formula (I) in the Summary section.

Embodiments of the invention include compounds wherein: (a) R<sub>1</sub> is  
 5 bromo or chloro; (b) R<sub>2</sub> is fluoro; (c) R<sub>3</sub> is H; (d) each of R<sub>2</sub> and R<sub>3</sub> is H;  
 (e) each of R<sub>2</sub> and R<sub>3</sub> is fluoro; (f) R<sub>1</sub> is bromo; (g) each of R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> is  
 fluoro; (h) R<sub>2</sub> is nitro; (i) R<sub>3</sub> is H; (j) R<sub>4</sub> is chloro; (k) R<sub>4</sub> is methyl; (l) R<sub>5</sub> is H;  
 (m) R<sub>5</sub> is CH<sub>3</sub>; (n) X<sub>1</sub> is O or S; (o) X<sub>1</sub> is NH or NCH<sub>3</sub>; (p) X<sub>2</sub> is OH, SH, or  
 NH<sub>2</sub>; (q) X<sub>2</sub> is OH; (r) X<sub>2</sub> is NHR<sub>E</sub>; (s) R<sub>4</sub> is H; (t) R<sub>4</sub> is chloro or methyl; or  
 10 combinations thereof.

Preferably, where one of the substituents on a heterocyclic radical is an  
 alkenyl or alkynyl group, the double or triple bond, respectively, is not adjacent  
 the point of attachment when it is a heteroatom. For example, in such a  
 situation, the substituent is preferably prop-2-ynyl, or but-2 or 3-enyl, and less  
 15 preferably prop-1-ynyl or but-1-enyl.

Examples of compounds include: [5-fluoro-2-(1H-tetrazol-5-yl)-  
 phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(1H-tetrazol-5-yl)-  
 phenyl]-(4-iodo-2-methyl-phenyl)-amine; (4-iodo-2-methyl-phenyl)-[2,3,4-  
 trifluoro-6-(1H-tetrazol-5-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(1H-  
 20 tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(1H-  
 tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-  
 dihydro-oxazol-2-yl)-5-fluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-  
 dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-  
 phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3,4-trifluoro-  
 25 phenyl]-(4-iodo-2-methyl-phenyl)-amine; [4-bromo-6-(4,4-dimethyl-4,5-  
 dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-  
 (4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-4-nitro-phenyl]-(4-iodo-2-  
 methyl-phenyl)-amine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-  
 [1,3,4]thiadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-  
 30 [1,3,4]thiadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-  
 phenyl]-[1,3,4]thiadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-  
 phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-

phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ol.

Further examples include: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-

thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-  
 [1,3,4]thiadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-  
 phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-  
 phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-  
 5 methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4-difluoro-2-(4-  
 iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4,5-  
 trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-  
 [5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-  
 [1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-  
 10 phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-  
 phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-  
 phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-  
 methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[5-bromo-3,4-  
 difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol;  
 15 and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-  
 [1,2,4]triazole-3-thiol.

Additional examples are: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-  
 phenyl]-isothiazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-  
 phenyl]-isothiazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-  
 20 phenyl]-isothiazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-  
 phenylamino)-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-  
 phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-  
 phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-  
 phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-  
 25 phenylamino)-phenyl]-isoxazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-  
 methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-  
 phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-  
 phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-  
 phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-  
 30 phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-  
 methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-  
 phenylamino)-5-nitro-phenyl]-1H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-

phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1-methyl-1H-pyrazol-3-ol.

The invention also features compounds such as: 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4,5-trifluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-5-bromo-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-5-nitro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 3-methyl-5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3H-[1,2,3]triazol-4-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 2-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-pyrazol-3-ol; 4-[5-



one; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-isoxazol-5-one.

Further compounds, where  $R_1$  can also be  $SO_2NR_G R_H$ , or  $R_1$  and  $R_2$  together with the benzene ring to which they are attached constitute an indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or  
 5 benzthioazole, include the following groups:

#### Group 1

- 10 (1) 2-Fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-N-methyl-benzenesulfonamide
- (3) 2,3-Difluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzenesulfonamide
- 15 (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-N-methyl-N-(3-morpholin-4-yl-propyl)-benzenesulfonamide
- (5) 2-Fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide
- 20 (6) N-(2-Dimethylamino-ethyl)-2-fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-phenylamino)-N-methyl-benzenesulfonamide

#### 25 Group 2

- (1) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (2) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro- benzenesulfonamide
- 30 (3) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

WO 01/05391

PCT/US00/18346

- (4) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide
- (5) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide
- 5 (6) 4-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 2b

- 10 (1) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (2) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-N-methyl-N-(3-morpholin-4-yl-propyl)-benzenesulfonamide
- (3) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- 15 (4) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide
- (5) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzenesulfonamide
- 20 (6) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-N-(3-piperidin-1-yl-propyl)-benzenesulfonamide

Group 3

- (1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide
- 25 (2) 2-Fluoro-5-(4-iodo-phenylamino)-4-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide
- (3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide
- 30 (4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide



- (5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide
- (6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

5

Group 4

- (1) 2-Fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (2) 2-Fluoro-4-(5-hydroxy-1,3,4-thiadiazol-2-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide
- (3) 2,3-Difluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (4) 2-Fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide
- (5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-benzenesulfonamide
- (6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-benzenesulfonamide

10

15

20

Group 5

- (1) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (2) 4-(5-Amino-1,3,4-thiadiazol-2-yl)-5-(4-iodo-phenylamino)-2-mercapto-benzenesulfonamide
- (3) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (4) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide
- (5) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide
- (6) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

25

30



- (2) 2-Fluoro-4-(3-hydroxy-isoxazol-5-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide
- (3) 2,3-Difluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- 5 (4) 2-Fluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide
- (5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-hydroxy-isoxazol-5-yl)-benzenesulfonamide
- (6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-hydroxy-isoxazol-5-yl)-  
10 benzenesulfonamide

Group 9

- (1) 5-(3-Amino-isoxazol-5-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- 15 (2) 4-(3-Amino-isoxazol-5-yl)-2-bromo-5-(4-iodo-phenylamino)-benzenesulfonamide
- (3) 5-(3-Amino-isoxazol-5-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (4) 5-(3-Amino-isoxazol-5-yl)-2-fluoro-4-(4-iodo-phenylamino)-  
20 benzenesulfonamide
- (5) 5-(3-Amino-isoxazol-5-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide
- (6) 5-(3-Amino-isoxazol-5-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

25

Group 10

- (1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide
- (2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-mercapto-isoxazol-5-yl)-  
30 benzenesulfonamide
- (3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

WO 01/05391

PCT/US00/18346

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

5 (6) 2-Bromo-5-(4-iodo-phenylamino)-4-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

#### Group 11

10 (1) 2-Fluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-hydroxy-isoxazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

15 (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-hydroxy-isoxazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

20 (6) 2-Bromo-4-(3-hydroxy-isoxazol-4-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

#### Group 12

(1) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

25 (2) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

(3) 5-(3-Amino-isoxazol-4-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

30 (4) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(5) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 4-(3-Amino-isoxazol-4-yl)-2-chloro-5-(4-iodo-phenylamino)-  
benzenesulfonamide

Group 13

- 5 (1) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-  
benzenesulfonamide
- (2) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-  
benzenesulfonamide
- (3) 5-(3-Amino-isoxazol-4-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-  
10 benzenesulfonamide
- (4) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-  
benzenesulfonamide"
- (5) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-phenylamino)-  
benzenesulfonamide
- 15 (6) 4-(3-Amino-isoxazol-4-yl)-2-chloro-5-(4-iodo-phenylamino)-  
benzenesulfonamide

Group 14

- (1) 5-(2-Amino-5H-pyrrol-3-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-  
20 benzenesulfonamide
- (2) 5-(2-Amino-5H-pyrrol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-  
benzenesulfonamide
- (3) 5-(2-Amino-5H-pyrrol-3-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-  
benzenesulfonamide
- 25 (4) 5-(2-Amino-5H-pyrrol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-  
benzenesulfonamide
- (5) 5-(2-Amino-5H-pyrrol-3-yl)-2-fluoro-4-(4-iodo-phenylamino)-  
benzenesulfonamide
- (6) 4-(2-Amino-5H-pyrrol-3-yl)-2-chloro-5-(4-iodo-phenylamino)-  
30 benzenesulfonamide

Group 15

- (1) 2-Fluoro-5-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-benzenesulfonamide
- (3) 2,3-Difluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-benzenesulfonamide
- (5) 2-Fluoro-5-{5-hydroxy-1-[3-(4-methyl-piperazin-1-yl)-propyl]-1H-pyrazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide
- (6) 2-Fluoro-4-(5-hydroxy-1H-pyrazol-4-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 16

- (1) 2-Fluoro-5-(5-hydroxy-3-methyl-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide
- (3) 2,3-Difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide
- (5) 2-Fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide
- (6) 2-Fluoro-5-{5-hydroxy-3-[2-(2-methoxy-ethoxy)-ethyl]-3H-1,2,3-triazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide

Group 17

- (1) 2-Fluoro-5-(5-hydroxy-3-methyl-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

- (2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)- benzenesulfonamide
- (3) 2,3-Difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide
- 5 (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide
- (5) 2-Fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide
- (6) 2-Fluoro-5-{5-hydroxy-3-[2-(2-methoxy-ethoxy)-ethyl]-3H-1,2,3-triazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide
- 10

Group 18

- (1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide
- 15 (2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide
- (3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide
- (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide
- 20 (5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide
- (6) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

25

Group 19

- (1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)- benzenesulfonamide
- (2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)- benzenesulfonamide
- 30 (3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

- (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide
- (5) 5-[4-(2-Dimethylamino-ethyl)-5-oxo-4,5-dihydro-tetrazol-1-yl]-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide
- 5 (6) 2-Fluoro-5-(4-iodo-phenylamino)-4-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

Group 20

- 10 (1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide
- (2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide
- (3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide
- 15 (4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide
- (5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide
- 20 (6) 2-Fluoro-5-(4-iodo-phenylamino)-4-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

Group 21

- (1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide
- 25 (2) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide
- (3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide
- 30 (4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide



(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-N-methyl-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

5

Group 22

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(2) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

10

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

15

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

20 Group 23

(1) 5-[6-(4-Iodo-2-methyl-phenylamino)-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-Iodo-phenylamino)-benzofuran-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoxazol-5-yl]-1,3,4-oxadiazol-2-ol

25

(4) 5-[5-(4-Iodo-phenylamino)-benzofuran-6-yl]-1,3,4-oxadiazol-2-ol

(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-1,3-dihydro-isobenzofuran-5-yl]-1,3,4-oxadiazol-2-ol

(6) 5-[6-(2-Chloro-4-iodo-phenylamino)-1-methyl-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol

30

Group 24

- (1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol
- (2) 5-[6-(4-Iodo-phenylamino)-benzo[b]thiophen-5-yl]-1,3,4-oxadiazol-2-ol
- 5 (3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol
- (4) 5-[5-(4-Iodo-phenylamino)-benzo[b]thiophen-6-yl]-1,3,4-oxadiazol-2-ol
- (5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-1,3-dihydro-benzo[c]thiophen-5-yl]-1,3,4-oxadiazol-2-ol
- 10 (6) 5-[6-(2-Chloro-4-iodo-phenylamino)-2-oxo-2,3-dihydro-1H-2*S*]-2,1,3-benzothiadiazol-5-yl]-1,3,4-oxadiazol-2-ol

Group 25

- (1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol
- 15 (2) 5-[6-(4-Iodo-phenylamino)-1H-indol-5-yl]-1,3,4-oxadiazol-2-ol
- (3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol
- (4) 5-[5-(4-Iodo-phenylamino)-1H-indol-6-yl]-1,3,4-oxadiazol-2-ol
- 20 (5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-2,3-dihydro-1H-isoindol-5-yl]-1,3,4-oxadiazol-2-ol
- (6) 5-[5-(2-Chloro-4-iodo-phenylamino)-1H-indazol-6-yl]-1,3,4-oxadiazol-2-ol

Group 26

- 25 (1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol
- (2) 5-[6-(4-Iodo-phenylamino)-1H-indol-5-yl]-1,3,4-oxadiazol-2-ol
- (3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoxazol-5-yl]-1,3,4-oxadiazol-2-ol
- 30 (4) 5-[5-(4-Iodo-phenylamino)-benzoxazol-6-yl]-1,3,4-oxadiazol-2-ol
- (5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-2,3-dihydro-1H-isoindol-5-yl]-1,3,4-oxadiazol-2-ol

WO 01/05391

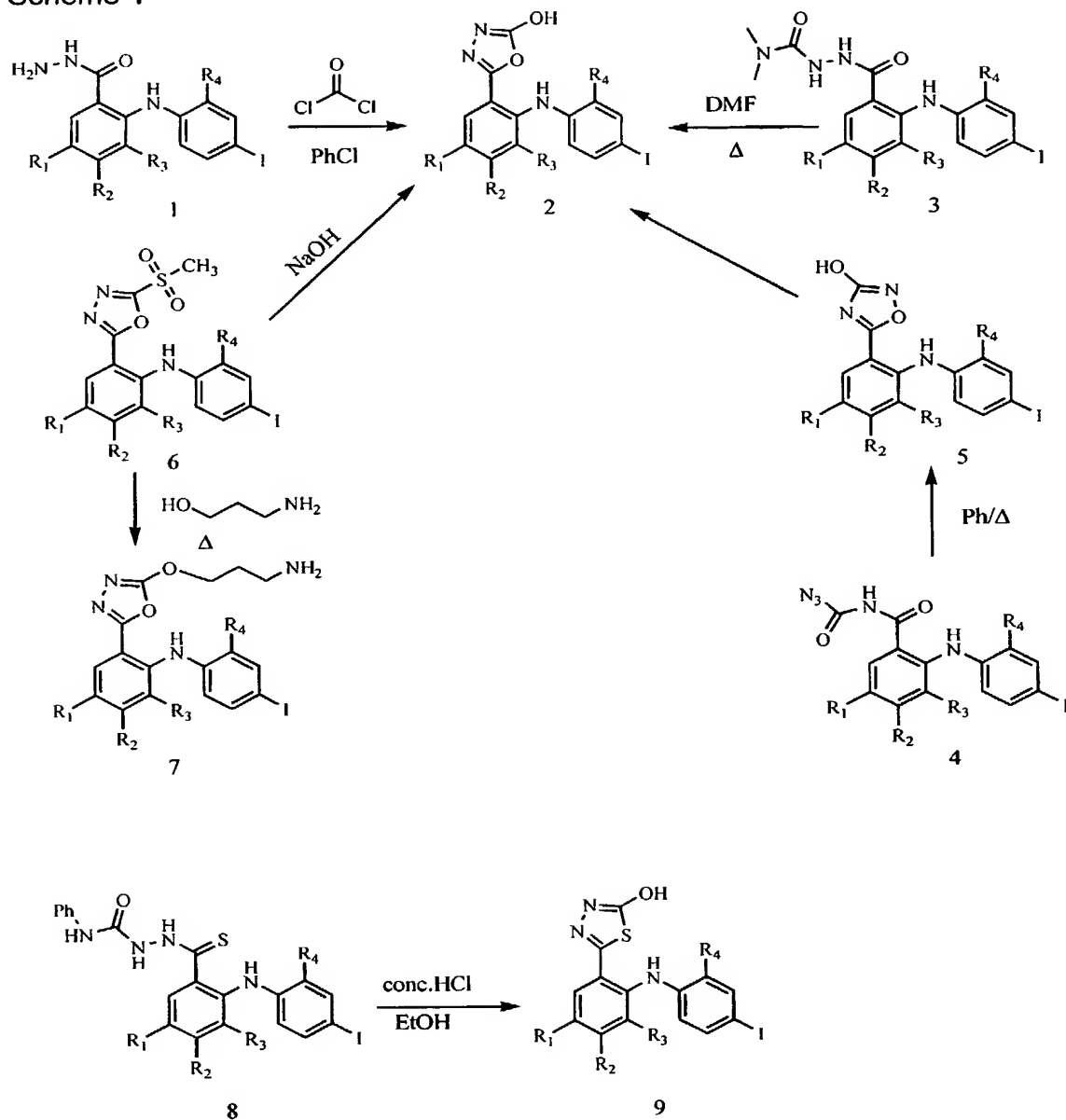
PCT/US00/18346

(6) 5-[5-(2-Chloro-4-iodo-phenylamino)-1H-indazol-6-yl]-1,3,4-oxadiazol-2-ol

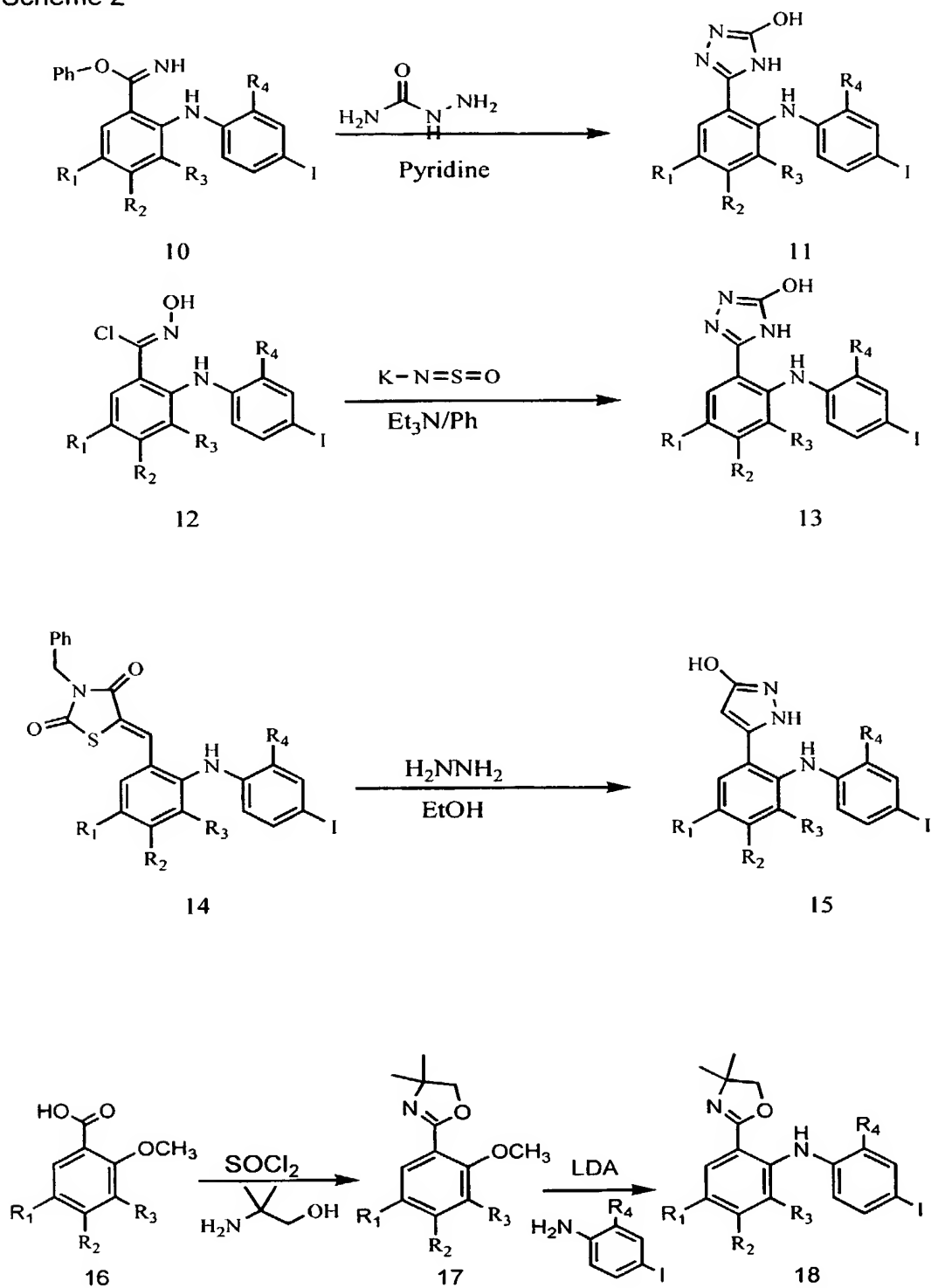
### C. Synthesis

The disclosed compounds can be synthesized according to Schemes 1-25 or analogous variants thereof. These synthetic strategies are further exemplified in Examples 1-8 below. The solvent between compounds 4 and 5 in Scheme 1 is toluene (PhMe).

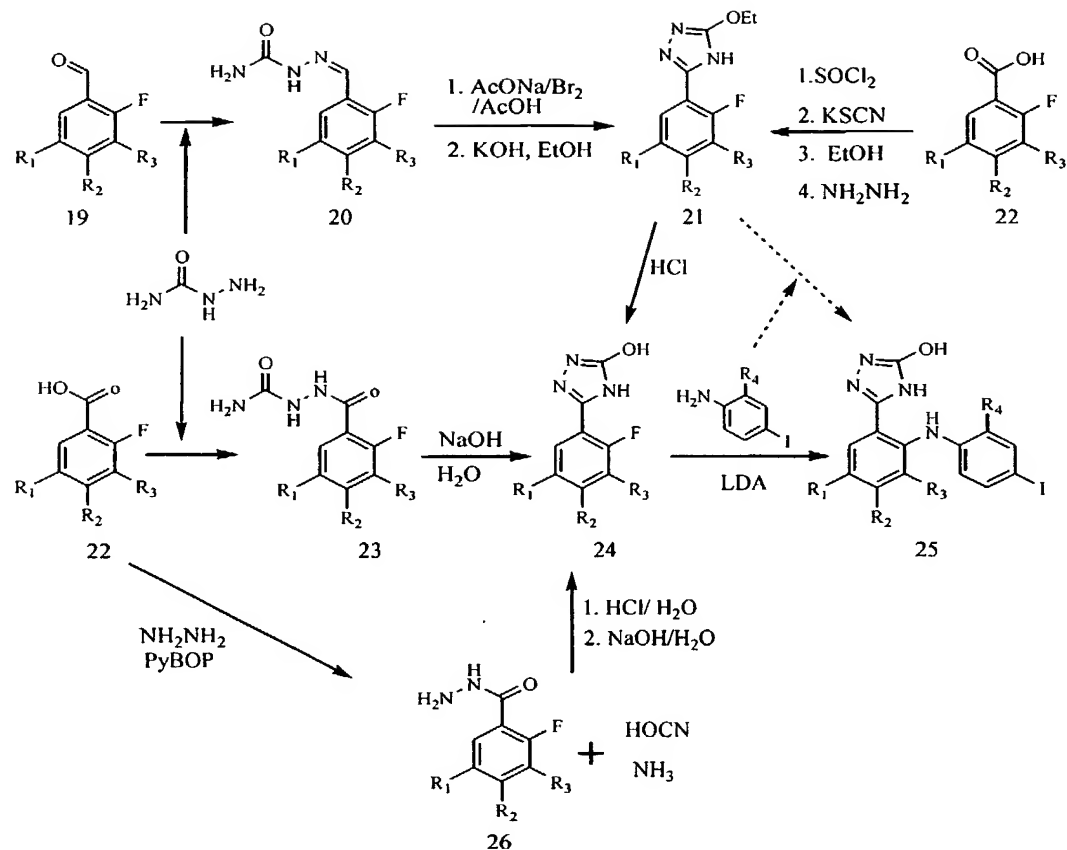
Scheme 1



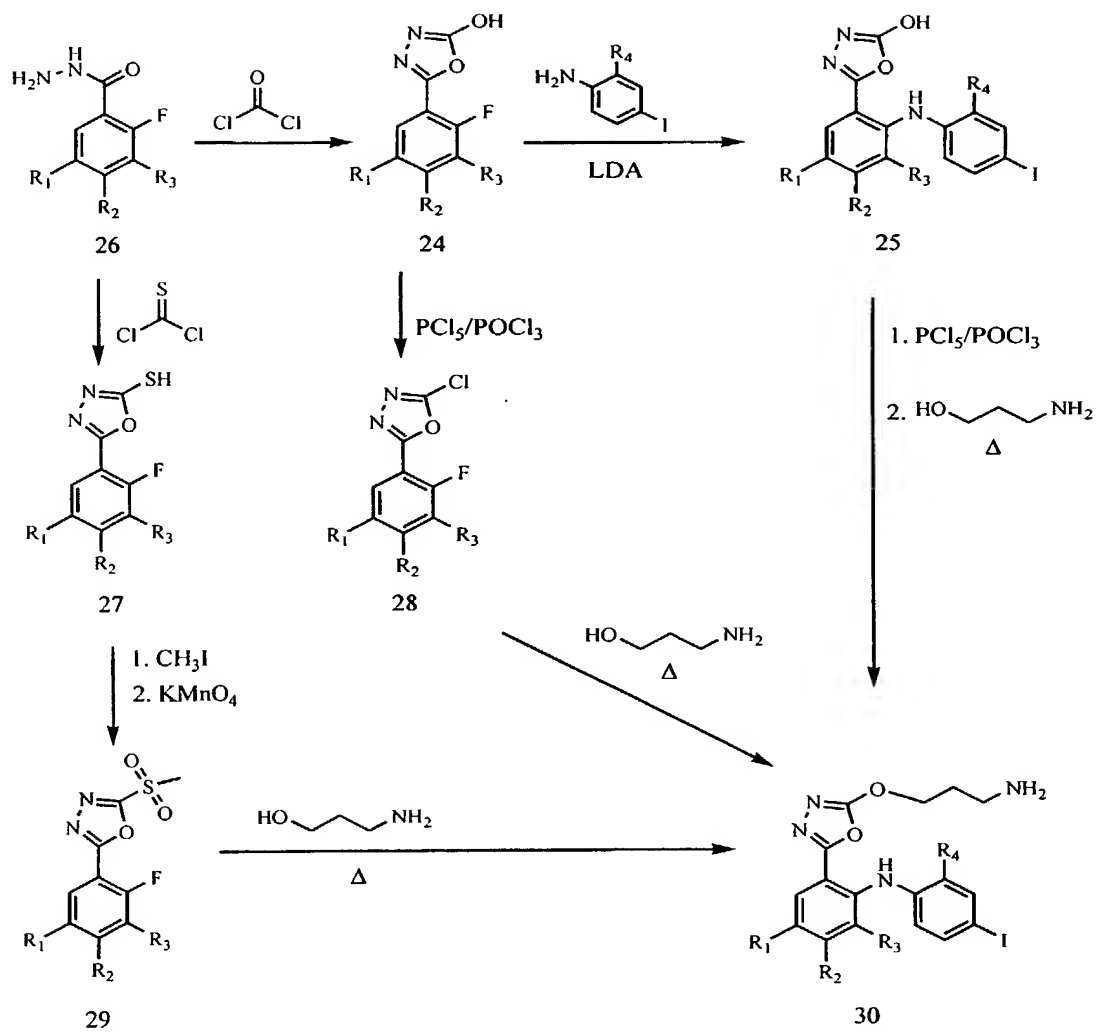
Scheme 2



Scheme 3

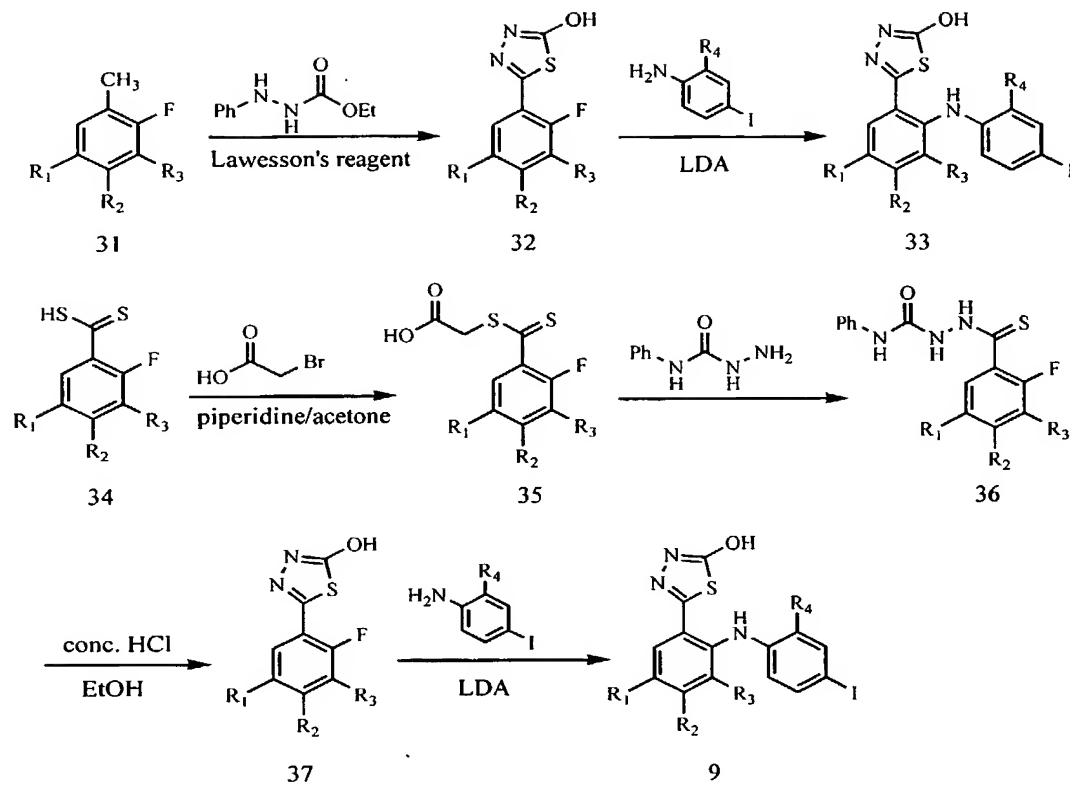


Scheme 4





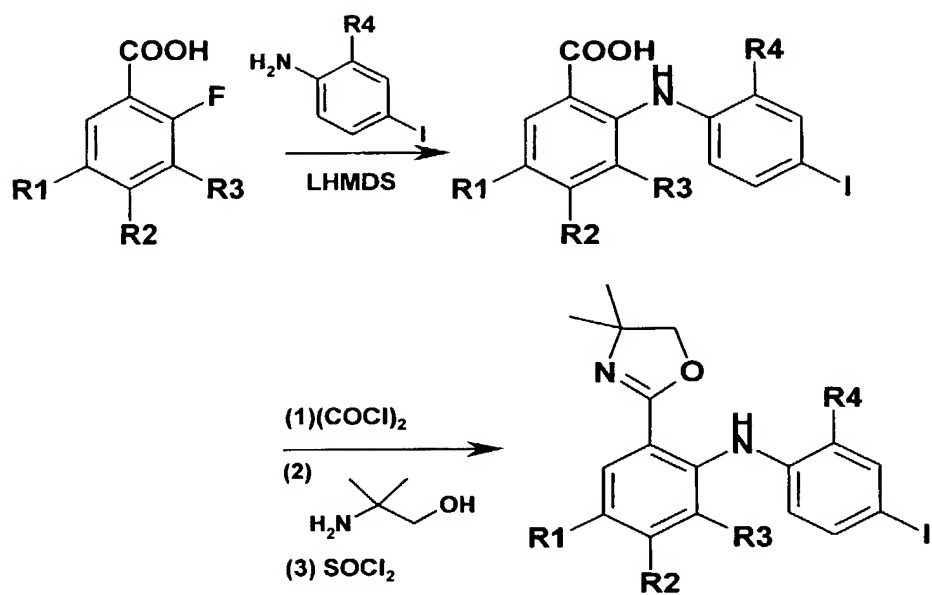
Scheme 5



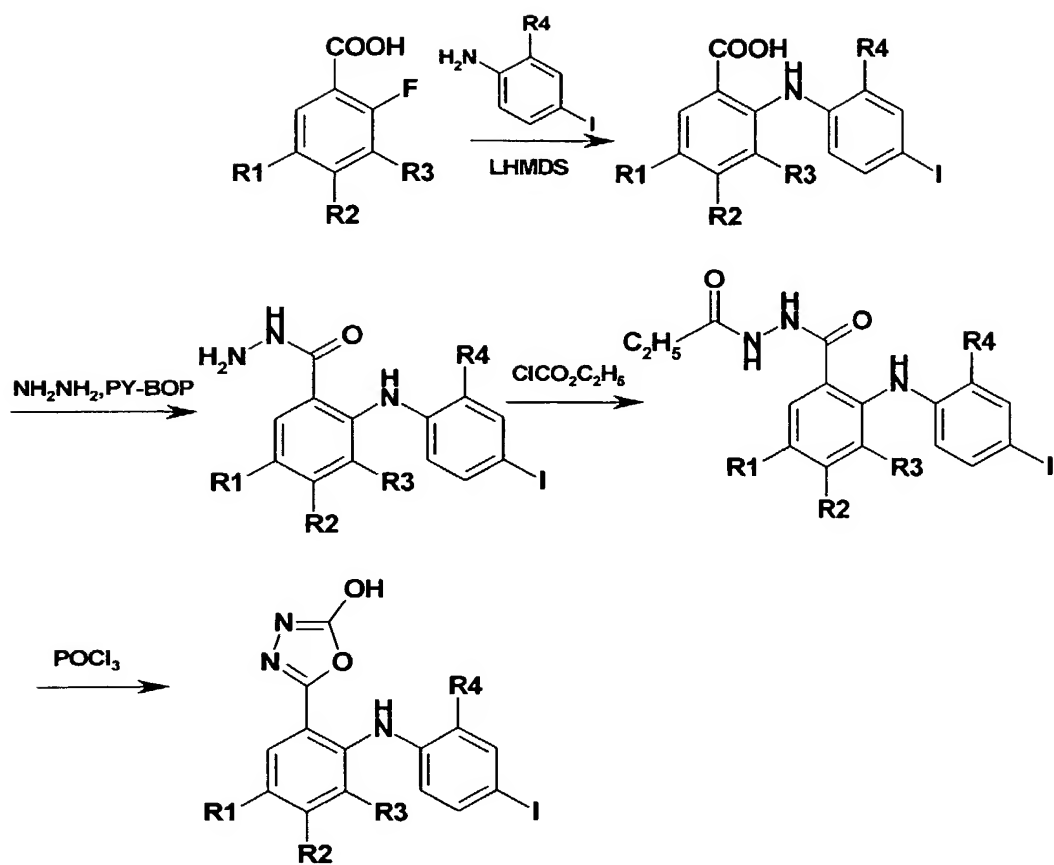
WO 01/05391

PCT/US00/18346

Scheme 6

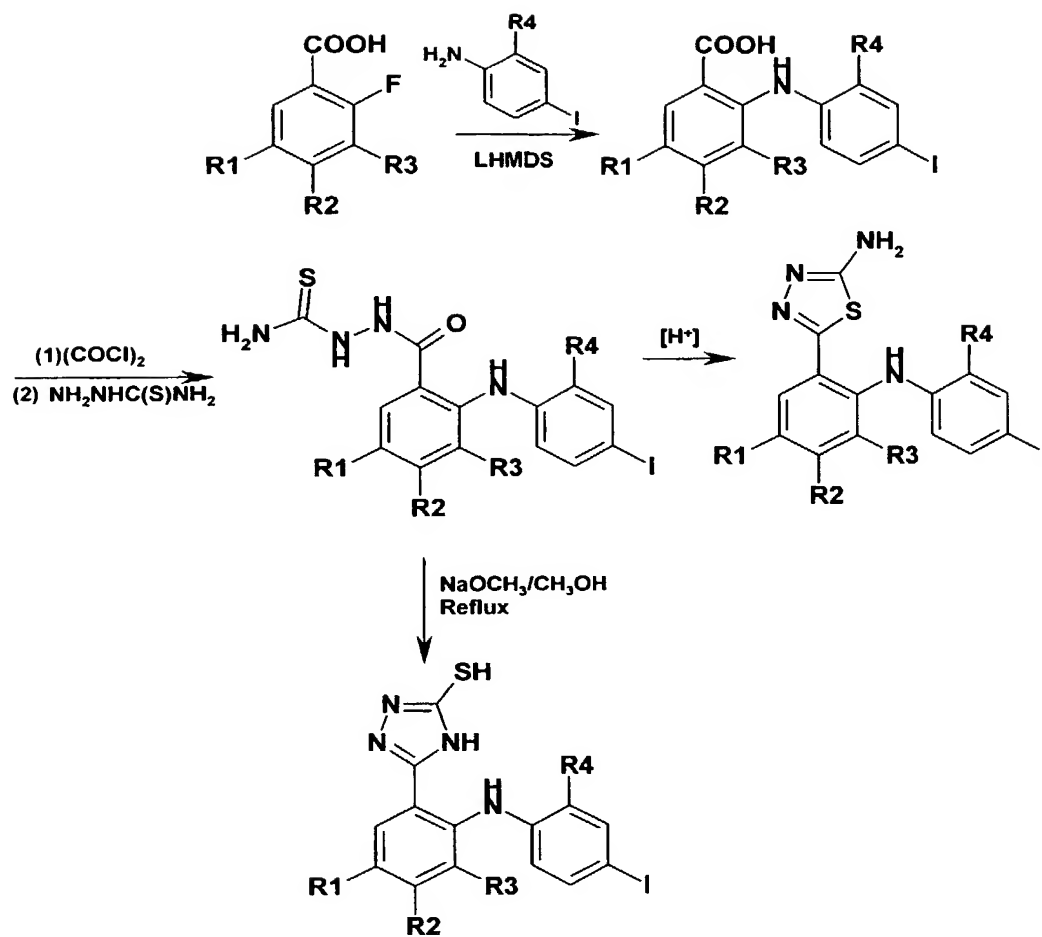


Scheme 7

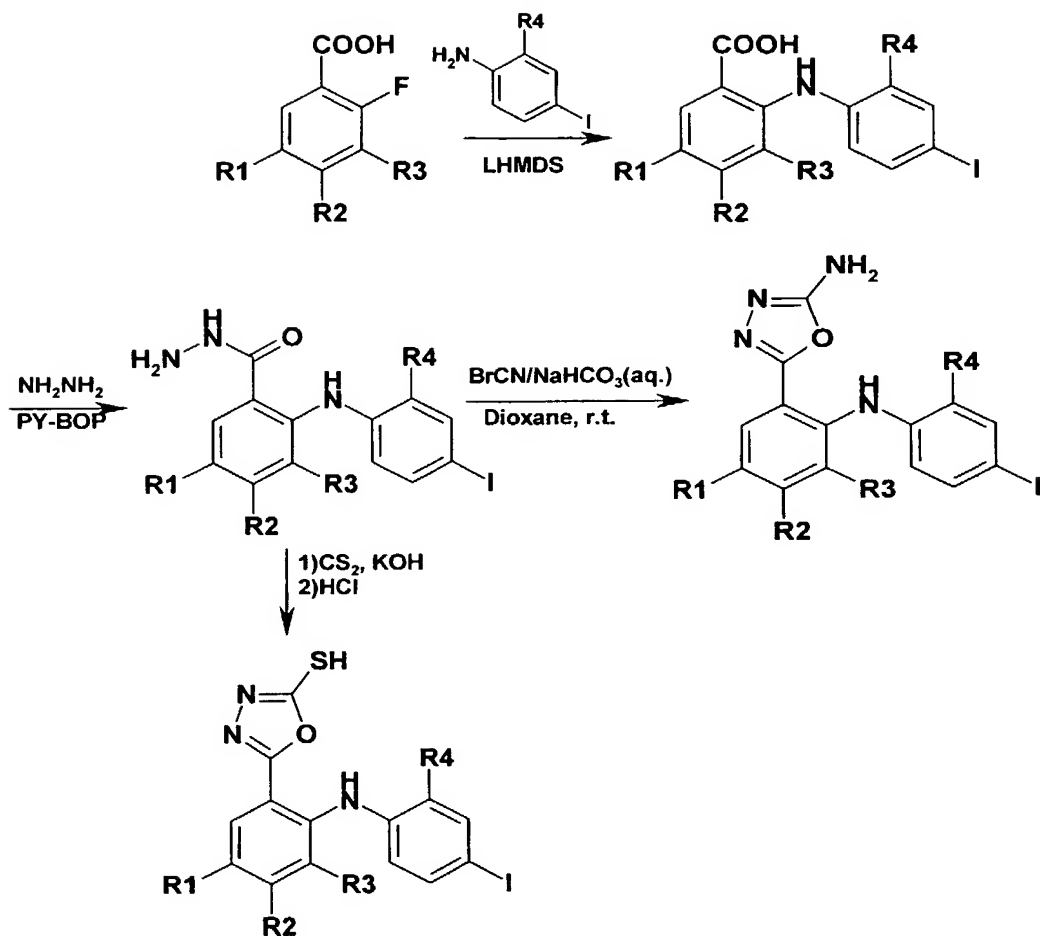




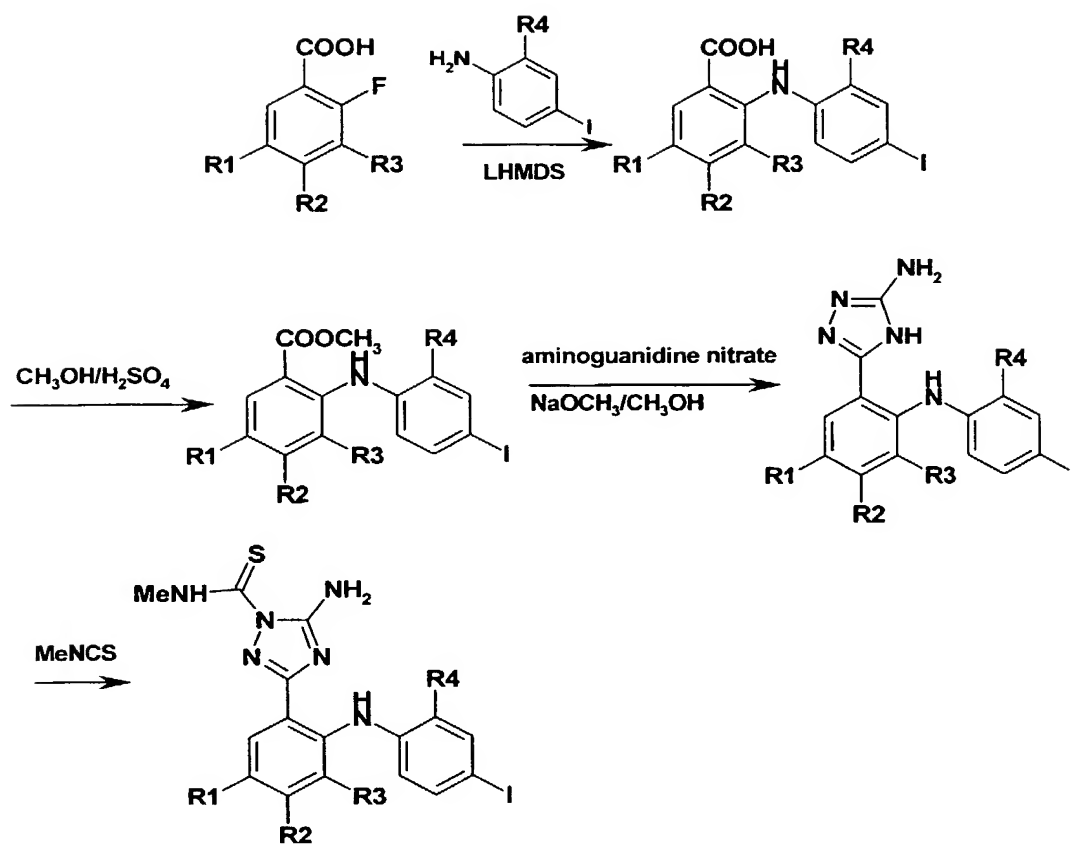
Scheme 9



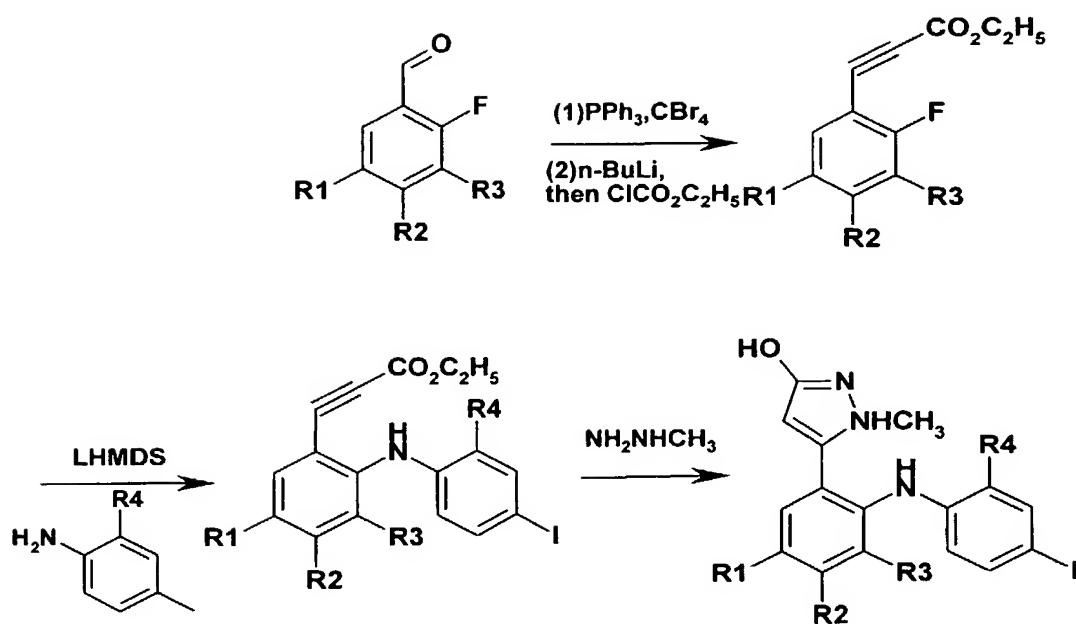
Scheme 10



Scheme 11



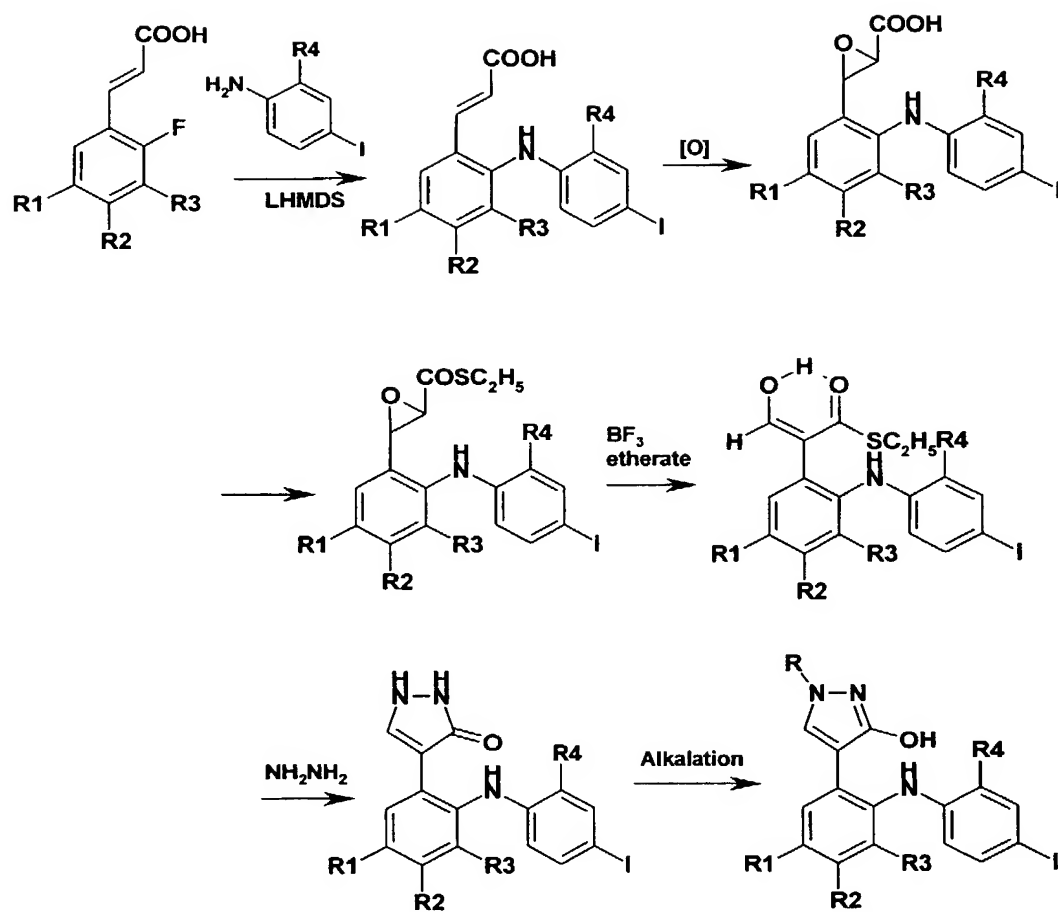
Scheme 12



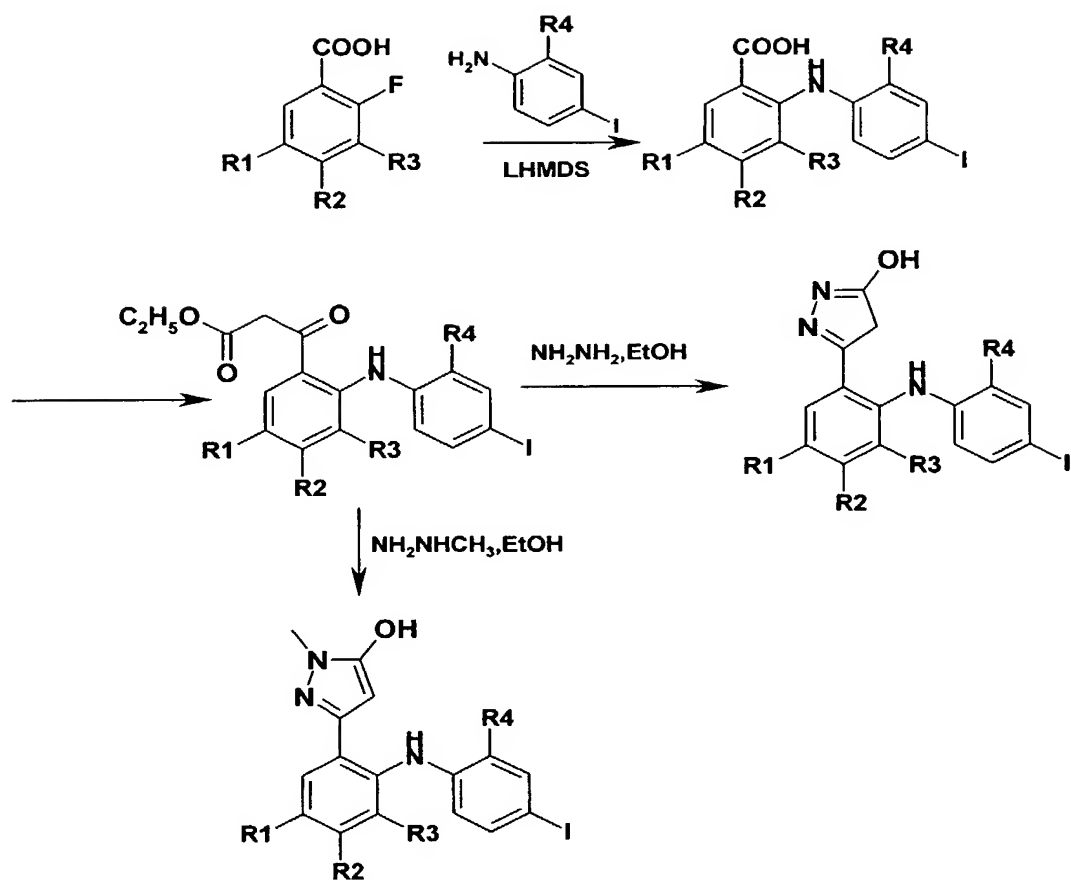




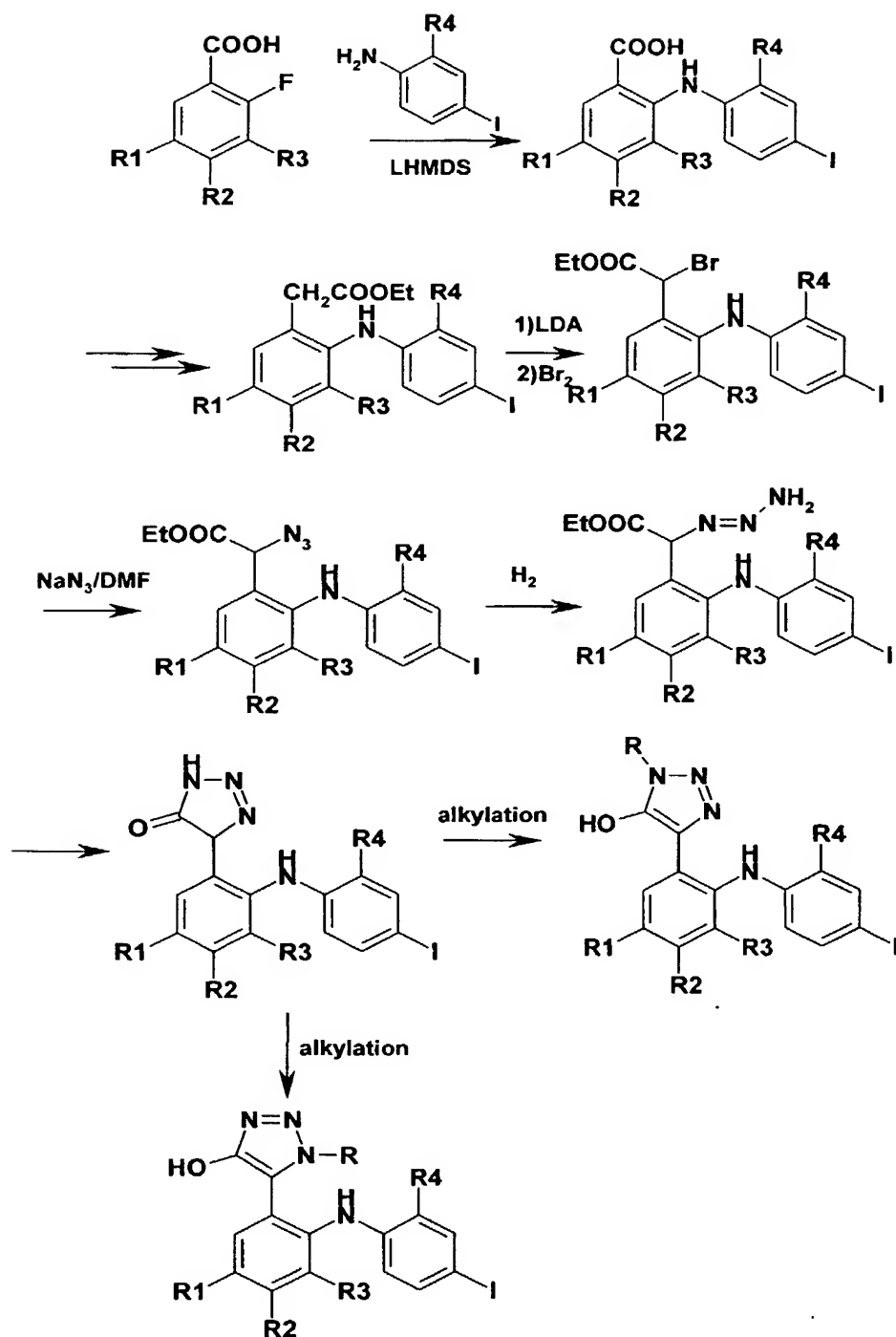
Scheme 14



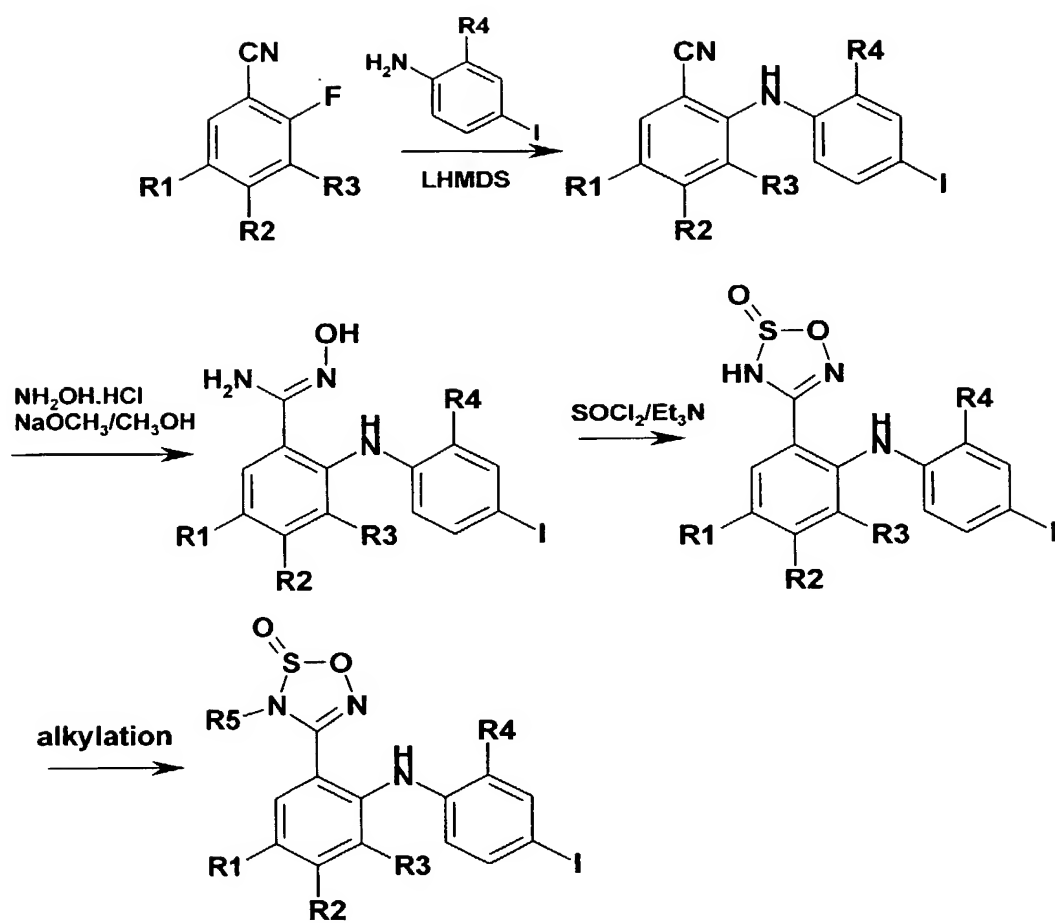
Scheme 15



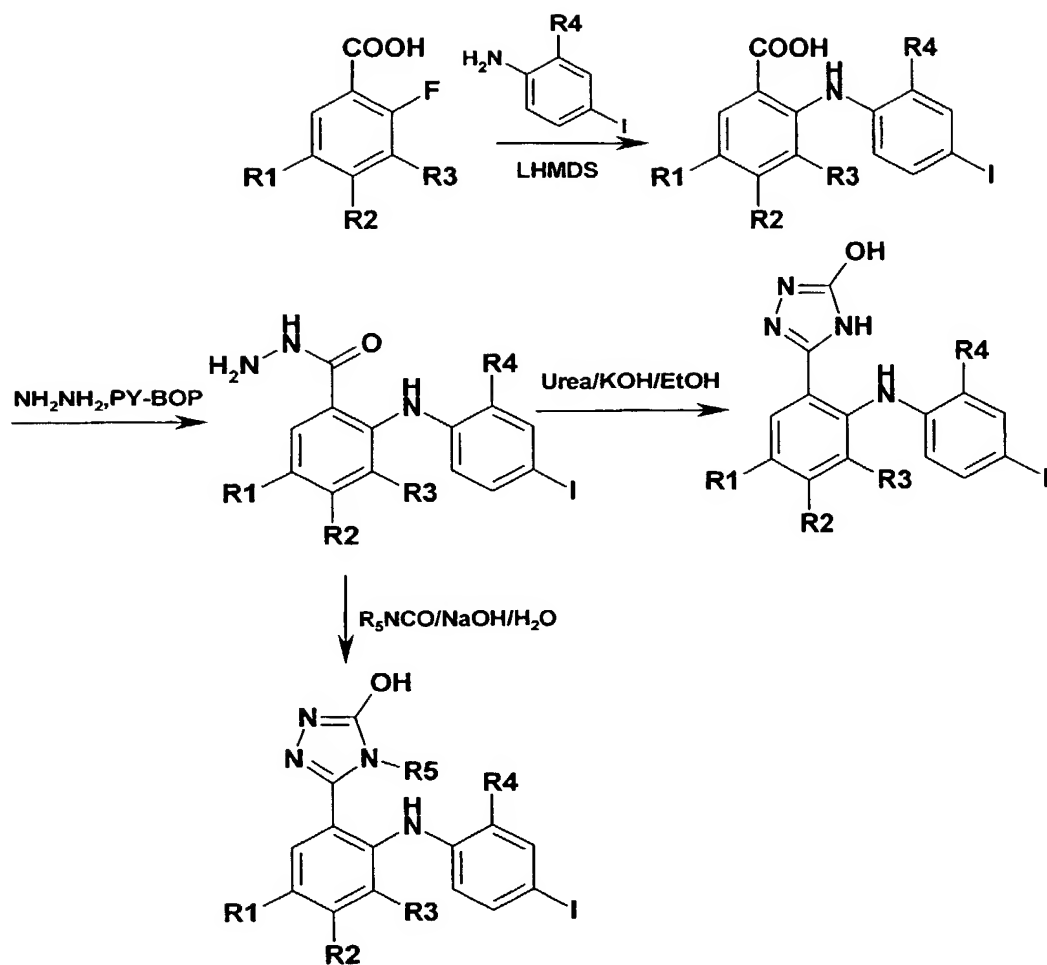
Scheme 16



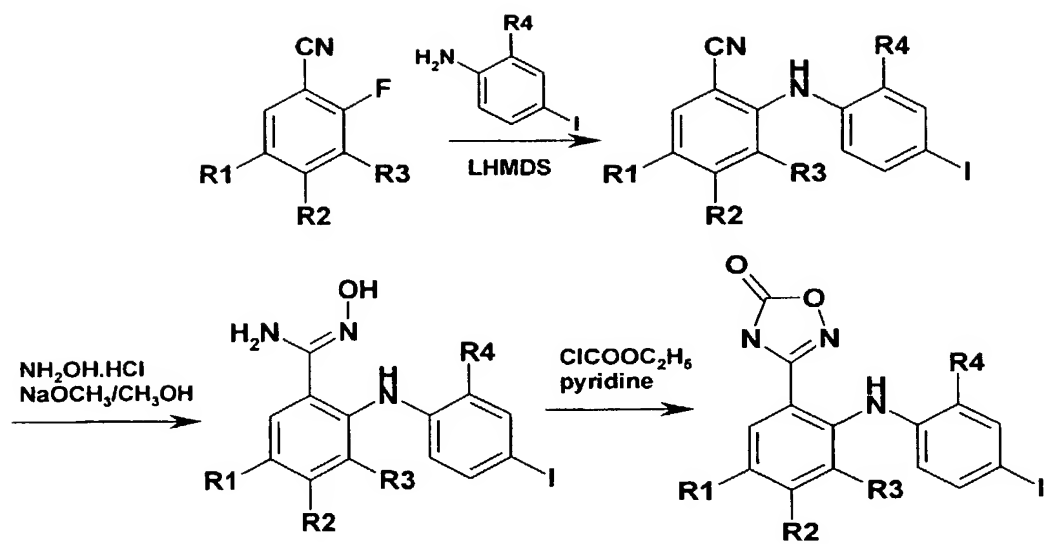
Scheme 17



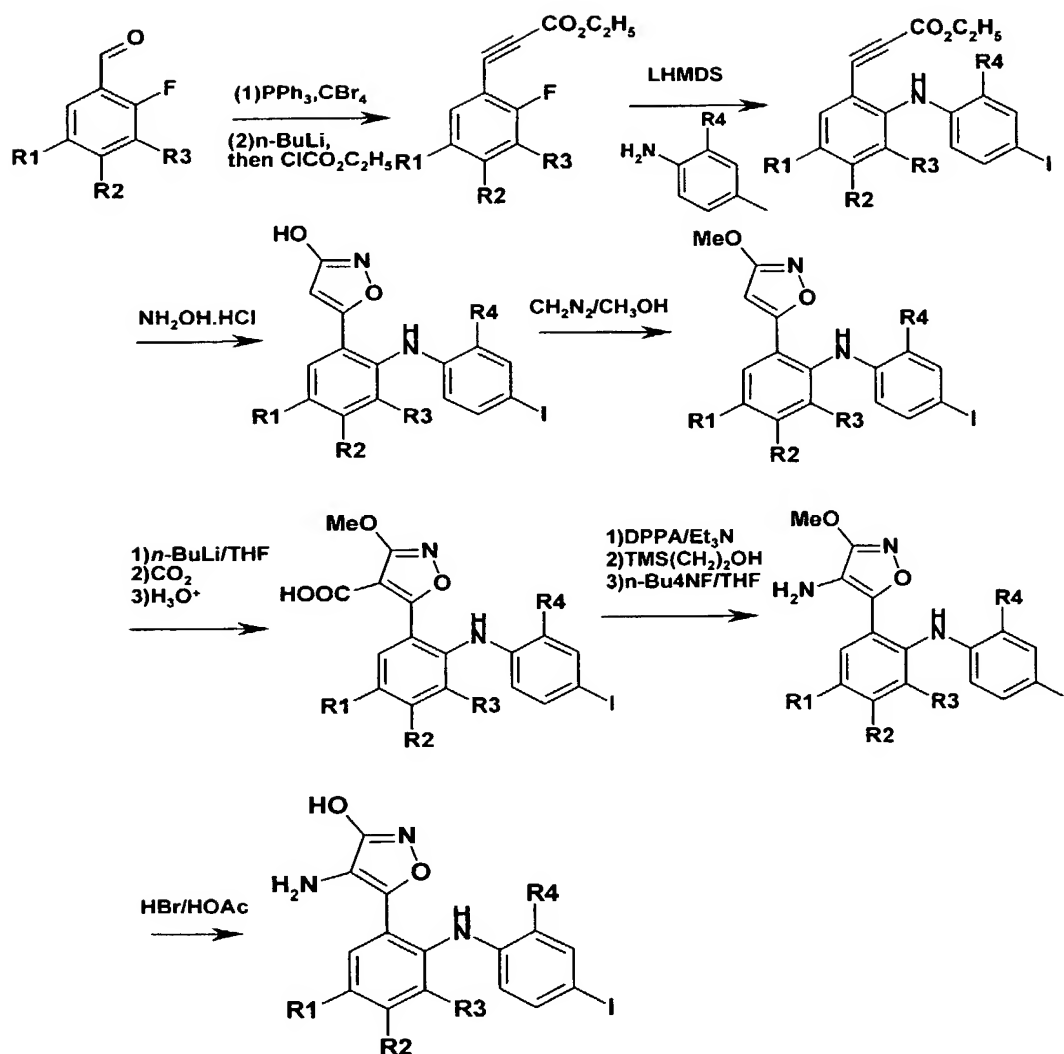
Scheme 18



Scheme 19

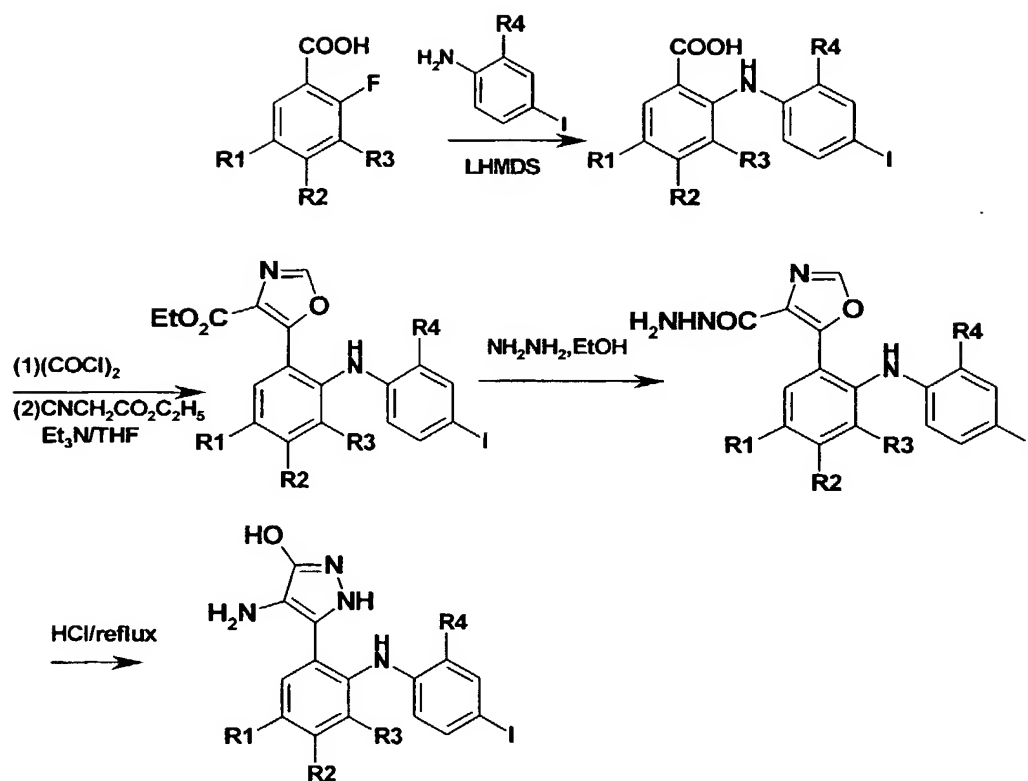


Scheme 20

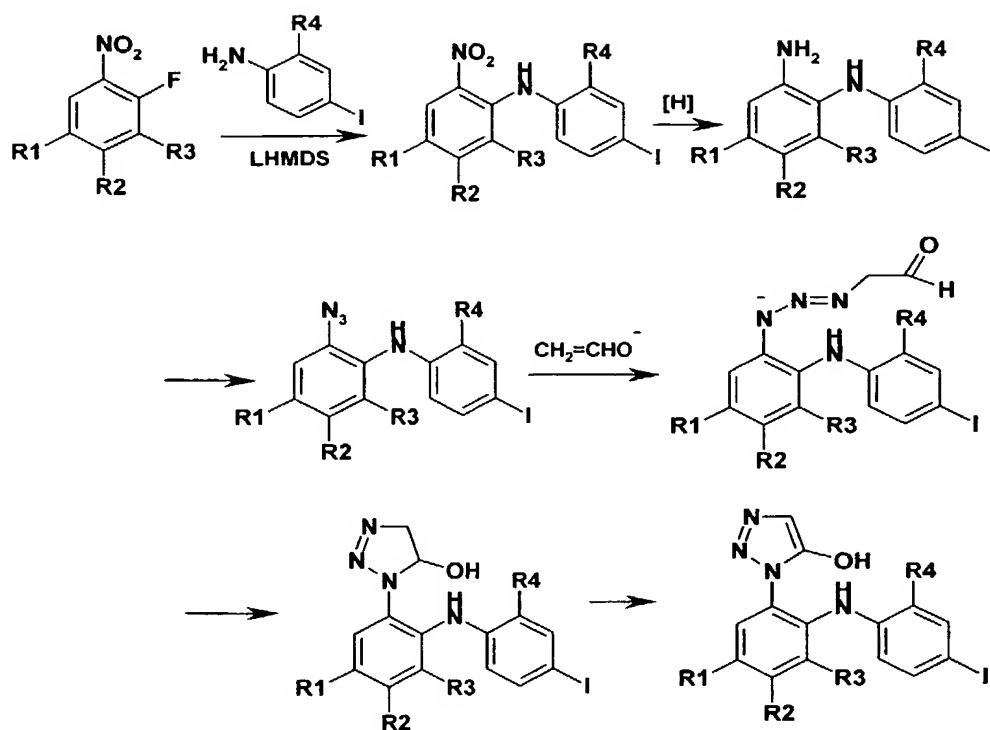




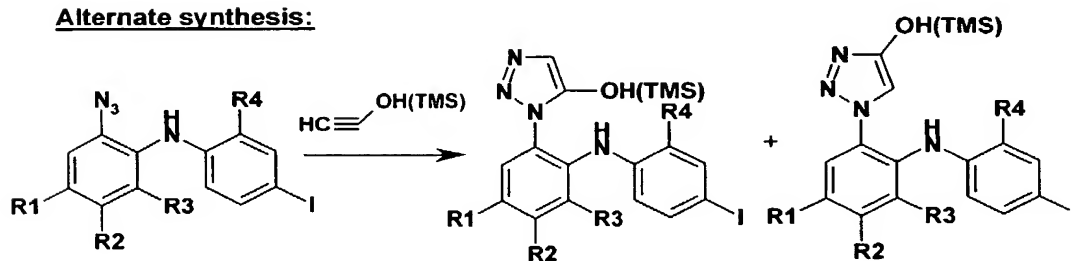
Scheme 21



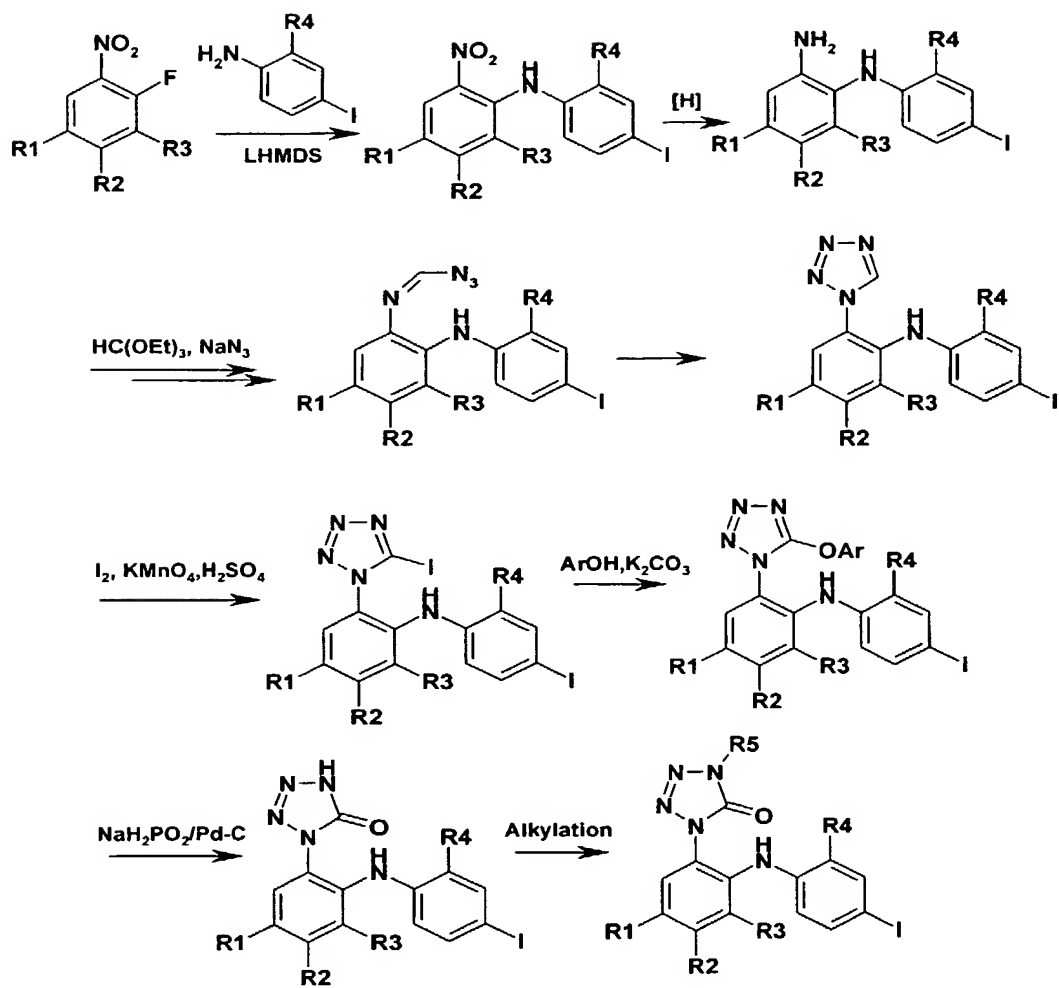
Scheme 22



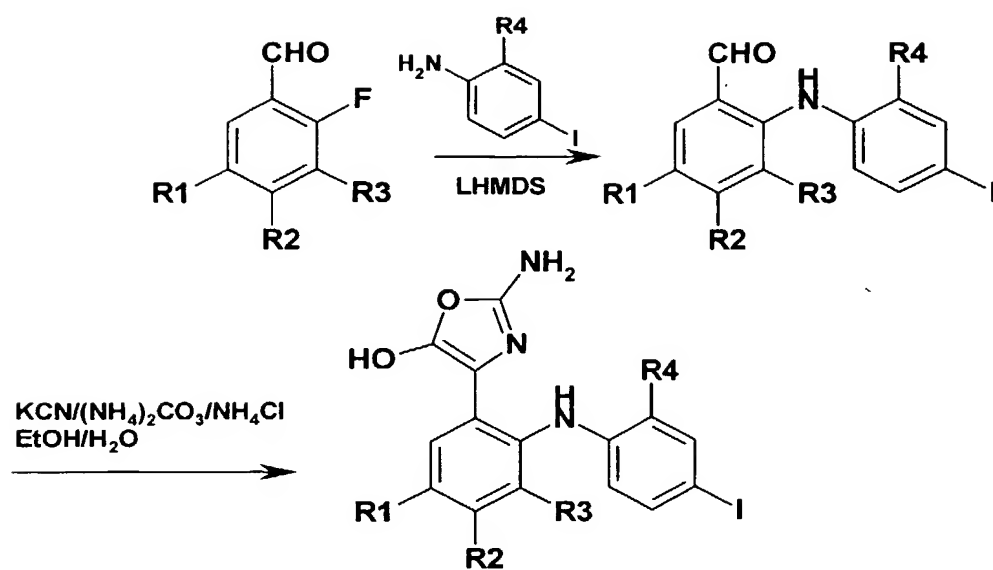
Alternate synthesis:



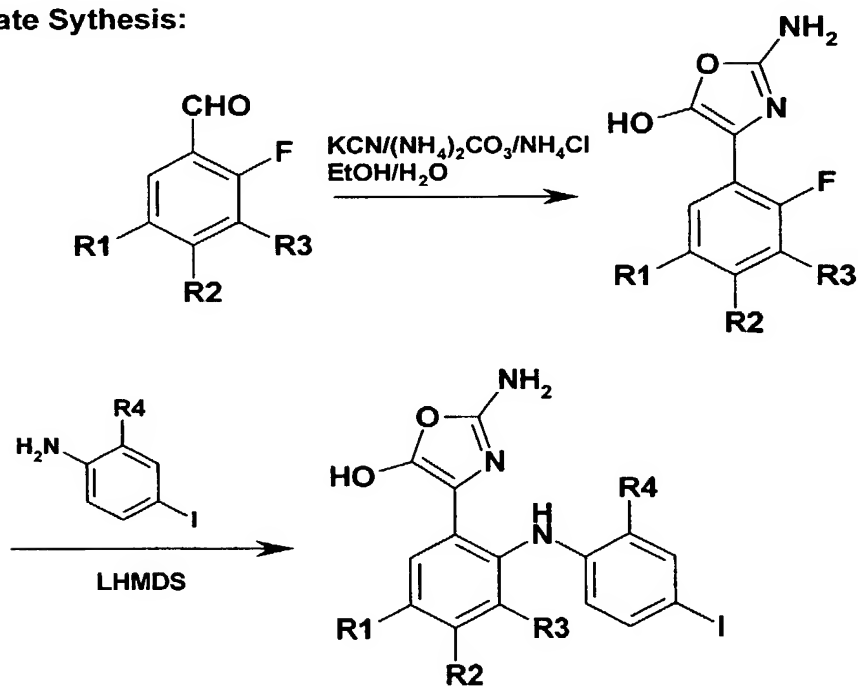
Scheme 23



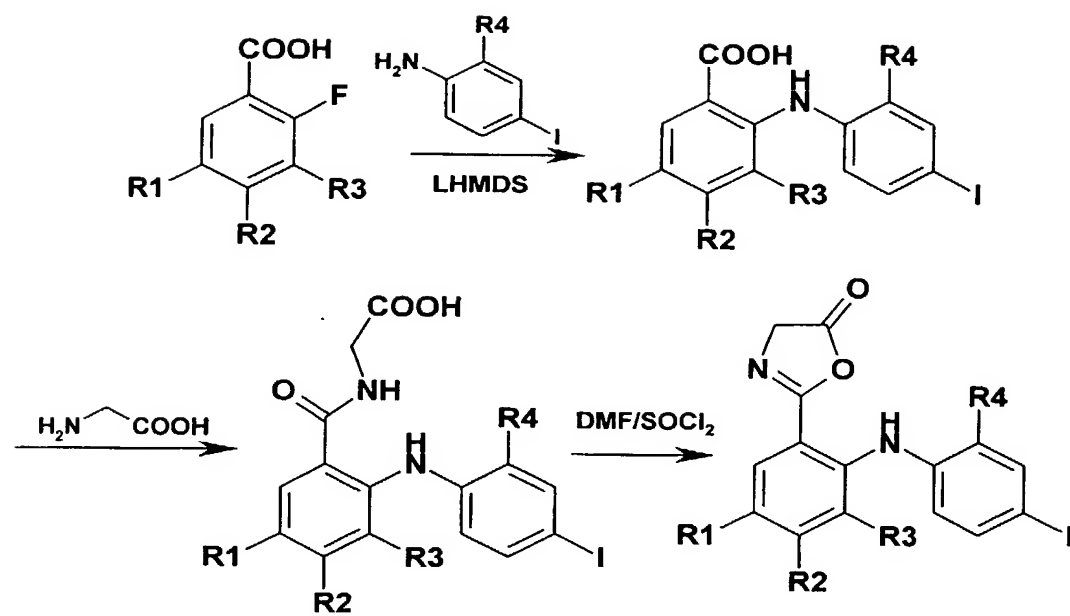
Scheme 24



Alternate Synthesis:



Scheme 25



## D. Uses

The disclosed compositions are useful as both prophylactic and therapeutic treatments for diseases or conditions relating to chronic pain, including neuropathic pain, as provided in the Summary section, as well as diseases or conditions modulated by the MEK cascade. For example, in one embodiment, the disclosed method relates to postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis, crush injury, constriction injury, tissue injury, post-surgical pain, arthritis pain, or limb amputation

For example, local injuries can be treated with local or topical administration. Chronic pain affecting the entire body, such as diabetic neuropathy can be treated with systemic administration (injection or orally) of a disclosed composition. Treatment for chronic pain (e.g., post-operative pain) confined to the lower body can be administered centrally, e.g., epidurally. Formulations and methods of administration can include the use of more than one MEK inhibitor, or a combination of a MEK inhibitor and another pharmaceutical agent, such as an anti-inflammatory, analgesic, muscle relaxing, or anti-infective agent. Preferred routes of administration are oral, intrathecal or epidural, subcutaneous, intravenous, intramuscular, and, for non-human mammals, intraplantar, and are preferably epidural.

### 1. Dosages

Those skilled in the art will be able to determine, according to known methods, the appropriate dosage for a patient, taking into account factors such as age, weight, general health, the type of pain requiring treatment, and the presence of other medications. In general, an effective amount will be between 0.1 and 1000 mg/kg per day, preferably between 1 and 300 mg/kg body weight, and daily dosages will be between 10 and 5000 mg for an adult subject of normal weight. Commercially available capsules or other

formulations (such as liquids and film-coated tablets) of 100 mg, 200 mg, 300 mg, or 400 mg can be administered according to the disclosed methods.

## 2. Formulations

- 5 Dosage unit forms include tablets, capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers adapted for subdivision into individual doses. Dosage unit forms can also be adapted for various methods of administration, including controlled release formulations, such as subcutaneous implants.
- 10 Administration methods include oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical, local (drops, powders, ointments, gels, or cream), and by inhalation (a buccal or nasal spray).

- Parenteral formulations include pharmaceutically acceptable aqueous or nonaqueous solutions, dispersion, suspensions, emulsions, and sterile powders for the preparation thereof. Examples of carriers include water, ethanol, polyols (propylene glycol, polyethylene glycol), vegetable oils, and injectable organic esters such as ethyl oleate. Fluidity can be maintained by the use of a coating such as lecithin, a surfactant, or maintaining appropriate particle size. Carriers for solid dosage forms include (a) fillers or extenders, (b) binders, (c) humectants, (d) disintegrating agents, (e) solution retarders, (f) absorption accelerators, (g) adsorbants, (h) lubricants, (i) buffering agents, and (j) propellants.
- 20

- Compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents; antimicrobial agents such as parabens, chlorobutanol, phenol, and sorbic acid; isotonic agents such as a sugar or sodium chloride; absorption-prolonging agents such as aluminum monostearate and gelatin; and absorption-enhancing agents.
- 25

### 3. Related compounds

The invention provides the disclosed compounds and closely related, pharmaceutically acceptable forms of the disclosed compounds, such as salts, esters, amides, hydrates or solvated forms thereof; masked or protected forms; and racemic mixtures, or enantiomerically or optically pure forms.

Pharmaceutically acceptable salts, esters, and amides include carboxylate salts (e.g., C<sub>1-8</sub> alkyl, cycloalkyl, aryl, heteroaryl, or non-aromatic heterocyclic), amino acid addition salts, esters, and amides which are within a reasonable benefit/risk ratio, pharmacologically effective, and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulfonate. These may include alkali metal and alkali earth cations such as sodium, potassium, calcium, and magnesium, as well as non-toxic ammonium, quaternary ammonium, and amine cations such as tetramethyl ammonium, methylamine, trimethylamine, and ethylamine. See, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977, 66:1-19 which is incorporated herein by reference. Representative pharmaceutically acceptable amides of the invention include those derived from ammonia, primary C<sub>1-6</sub> alkyl amines and secondary di (C<sub>1-6</sub> alkyl) amines. Secondary amines include 5- or 6-membered heterocyclic or heteroaromatic ring moieties containing at least one nitrogen atom and optionally between 1 and 2 additional heteroatoms. Preferred amides are derived from ammonia, C<sub>1-3</sub> alkyl primary amines, and di (C<sub>1-2</sub> alkyl)amines. Representative pharmaceutically acceptable esters of the invention include C<sub>1-7</sub> alkyl, C<sub>5-7</sub> cycloalkyl, phenyl, and phenyl(C<sub>1-6</sub>)alkyl esters. Preferred esters include methyl esters.

The invention also includes disclosed compounds having one or more functional groups (e.g., hydroxyl, amino, or carboxyl) masked by a protecting group. Some of these masked or protected compounds are pharmaceutically



acceptable; others will be useful as intermediates. Synthetic intermediates and processes disclosed herein, and minor modifications thereof, are also within the scope of the invention.

## 5 HYDROXYL PROTECTING GROUPS

Hydroxyl protecting groups include: ethers, esters, and protection for 1,2- and 1,3-diols. The ether protecting groups include: methyl, substituted methyl ethers, substituted ethyl ethers, substituted benzyl ethers, silyl ethers and conversion of silyl ethers to other functional groups.

### 10 Substituted Methyl Ethers

Substituted methyl ethers include: methoxymethyl, methylthiomethyl, *t*-utylthiomethyl, (phenyldimethylsilyl) methoxymethyl, benzyloxymethyl, *p*-ethoxybenzyloxymethyl, (4-methoxyphenoxy) methyl, guaiacolmethyl, *t*-butoxymethyl, 4-pentenylloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 15 2,2,2-trichloroethoxymethyl, bis(2-chloro-ethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydro-pyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothio-pyranyl, 4-methoxytetrahydrothiopyranyl *S,S*-dioxido, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, 20 tetrahydrofuranyl, tetrahydrothiofuranyl, and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-ethanobenzofuran-2-yl.

### Substituted Ethyl Ethers

Substituted ethyl ethers include: 1-ethoxyethyl, 1-(2, chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-25 fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, and benzyl.

### Substituted Benzyl Ethers

Substituted benzyl ethers include: *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, 30 *p*-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p*, *p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl,  $\alpha$ -naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl,





$\alpha$ -methoxybenzylidene, 1-(*N,N*-dimethylamino)ethylidene derivative,  $\alpha$ -(*N,N*-dimethylamino) benzylidene derivative, and 2-oxacyclopentylidene.

## 5 PROTECTION FOR THE CARBOXYL GROUP

### ESTERS

Ester protecting groups include: esters, substituted methyl esters, 2-substituted ethyl esters, substituted benzyl esters, silyl esters, activated esters, miscellaneous derivatives, and stannyl esters.

#### 10 Substituted Methyl Esters

Substituted methyl esters include: 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxy-methyl, benzyloxymethyl, phenacyl, *p*-bromophenacyl,  $\alpha$ -methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and *N*-  
15 phthalimidomethyl.

#### 2-Substituted Ethyl Esters

2-Substituted ethyl esters include: 2,2,2-trichloroethyl, 2-haloethyl, 1-chloroalkyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2(*p*-nitrophenylsulfenyl)-ethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(2'-pyridyl)ethyl, 2-  
20 (diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, *t*-butyl, cyclopentyl, cyclohexyl, allyl, 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl,  $\alpha$ -methylcinnamyl, phenyl, *p*-(methylmercapto)-phenyl, and benzyl.

#### Substituted Benzyl Esters

Substituted benzyl esters include: triphenylmethyl, diphenylmethyl, 25 bis(*o*-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl, 5-dibenzo-suberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromylmethyl, 2,4,6-trimethylbenzyl, *p*-bromobenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfobenzyl, piperonyl, and 4-P-benzyl.

#### 30 Silyl Esters

Silyl esters include: trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-propyldimethylsilyl, phenyldimethylsilyl, and di- *t*-butylmethylsilyl.



### Assisted Cleavage

Protection via assisted cleavage includes: 2-methylthioethyl,  
2-methylsulfonyl ethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl,  
5 4-methylthiophenyl, 2,4-dimethyl-thiophenyl, 2-phosphonioethyl,  
2-triphenylphosphonioisopropyl, 1,1-dimethyl-2cyanoethyl, *m*-chloro-*p*-  
acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolyl-methyl, and  
2-(trifluoromethyl)-6-chromonylmethyl.

### Photolytic Cleavage

10 Photolytic cleavage methods use groups such as: *m*-nitrophenyl, 3,5-  
dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, and phenyl(*o*-  
nitrophenyl)methyl.

### Urea-Type Derivatives

Examples of of urea-type derivatives include: phenothiazinyl-(10)-carbonyl  
15 derivative, *N*'-*p*-toluenesulfonylaminocarbonyl, and *N*'-  
phenylaminothiocarbonyl.

### Miscellaneous Carbamates

In addition to the above, miscellaneous carbamates include: *t*-amyl, *S*-benzyl  
thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl,  
20 cyclopropylmethyl, *p*-decyloxy-benzyl, diisopropylmethyl, 2,2-  
dimethoxycarbonylvinyl, *o*-(*N,N*-dimethyl-carboxamido)-benzyl, 1,1-dimethyl-  
3(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethyl-propynyl, di(2-pyridyl)methyl,  
2-furanylmethyl, 2-iodoethyl, isobornyl, isobutyl, isonicotinyl, *p*(*p*'-  
methoxyphenyl- azo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-  
25 methyl-1-cyclopropyl- methyl, 1-methyl-(3,5-dimethoxyphenyl)ethyl, 1-methyl-  
1(*p*-henylazophenyl)- ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-  
pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-  
(trimethylammonium) benzyl, and 2,4,6-trimethylbenzyl.

## AMIDES

### Amides

Amides includes: *N*-formyl, *N*-acetyl, *N*-chloroacetyl, *N*-trichloroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridyl-carboxamide, *N*-benzoylphenylalanyl derivative, *N*-benzoyl, and *N*-*p*-phenylbenzoyl.

### Assisted Cleavage

Assisted cleavage groups include: *N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N*'-dithiobenzoyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl) propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine derivative, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, and 4,5-diphenyl-3-oxazolin-2-one.

### Cyclic Imide Derivatives

Cyclic imide derivatives include: *N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenyl-maleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, and 1-substituted 3,5-dinitro-4-pyridonyl.

## SPECIAL -NH PROTECTIVE GROUPS

Protective groups for –NH include: *N*-alkyl and *N*-aryl amines, imine derivatives, enamine derivatives, and *N*-hetero atom derivatives (such as *N*-metal, *N*-N, *N*-P, *N*-Si, and *N*-S), *N*-sulfenyl, and *N*-sulfonyl.

### *N*-Alkyl and *N*-Aryl Amines

*N*-alkyl and *N*-aryl amines include: *N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxyl]-methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), quaternary ammonium salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl,

*N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, and *N*-2-picolylamine *N*'-oxide.

#### Imine Derivatives

Imine derivatives include: *N*-1,1-dimethylthiomethylene, *N*-benzylidene,  
 5 *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene,  
*N*-[(2-pyridyl)mesityl]methylene, *N*-(*N*',*N*'-dimethylaminomethylene),  
*N,N*'-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene,  
*N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenyl-methylene, and  
*N*-cyclohexylidene.

#### 10 Enamine Derivative

An example of an enamine derivative is  
*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl).

#### *N*-Hetero Atom Derivatives

*N*-metal derivatives include: *N*-borane derivatives, *N*-diphenylborinic acid  
 15 derivative, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, and  
*N*-copper or *N*-zinc chelate. Examples of *N-N* derivatives include: *N*-nitro,  
*N*-nitroso, and *N*-oxide. Examples of *N-P* derivatives include:  
*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl,  
*N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, and *N*-diphenyl phosphoryl.  
 20 Examples of *N*-sulfenyl derivatives include: *N*-benzenesulfenyl,  
*N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl,  
*N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxy-benzenesulfenyl, *N*-  
 triphenylmethylsulfenyl, and *N*-3-nitropyridinesulfenyl. *N*-sulfonyl derivatives  
 include: *N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-  
 25 4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-  
 2,6-dimethyl-4-methoxy-benzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-  
 2,3,5,6-tetramethyl-4-methoxybenzene- sulfonyl, *N*-  
 4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-  
 2,6-dimethoxy- 4-methylbenzenesulfonyl, *N*-  
 30 2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl,



*N*- $\beta$ -trimethylsilylethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)-benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, and *N*-phenacylsulfonyl.

5            Disclosed compounds which are masked or protected may be prodrugs, compounds metabolized or otherwise transformed *in vivo* to yield a disclosed compound, e.g., transiently during metabolism. This transformation may be a hydrolysis or oxidation which results from contact with a bodily fluid such as blood, or the action of acids, or liver, gastrointestinal, or other enzymes.

10           Features of the invention are further described in the examples below.

## E. Examples

### BIOLOGICAL EXAMPLES

5

#### Example 1

#### **Effect of PD 198306 on streptozocin-induced static allodynia**

##### Animals

Male Sprague Dawley rats (250-300g), obtained from Bantin and  
 10 Kingman, (Hull, U.K.) were housed in groups of 3. All animals were kept under  
 a 12h light/dark cycle (lights on at 07h 00min) with food and water *ad libitum*.  
 All experiments were carried out by an observer blind to drug treatments.

##### Development of diabetes in the rat

15 Diabetes was induced in rats by a single i.p. injection of streptozocin  
 (50 mg/kg) as described previously (Courteix et al., 1993).

##### Evaluation of static allodynia

Mechanical hypersensitivity was measured using Semmes-Weinstein  
 20 von Frey hairs (Stoelting, Illinois, U.S.A.). Animals were placed into wire mesh  
 bottom cages allowing access to the underside of their paws. Animals were  
 habituated to this environment prior to the start of the experiment. Mechanical  
 hypersensitivity was tested by touching the plantar surface of the animals right  
 hind paw with von Frey hairs in ascending order of force ( 0.7, 1.2, 1.5, 2, 3.6,  
 25 5.5, 8.5, 11.8, 15.1 and 29g) for up to 6 sec. Once a withdrawal response was  
 established, the paw was re-tested, starting with the next descending von  
 Frey hair until no response occurred. The highest force of 29 g lifted the paw  
 as well as eliciting a response, thus represented the cut off point. The lowest  
 amount of force required to elicit a response was recorded as the paw  
 30 withdrawal threshold (PWT) in grams.



PD 198306	PD 198306
Pregabalin	Pregabalin
Vehicle	Vehicle
<b>Test</b>	<b>Test</b>

5

## RESULTS

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked streptozocin-induced static allodynia 1h after administration. In contrast, a single administration of PD 198306 (30mg/kg, p.o) had no effect on streptozocin-induced static allodynia 1h after administration (see below). However, after the compound had been administered twice more on the following day, it significantly blocked streptozocin-induced static allodynia 1h after the third administration. The effects had disappeared by the following day (see FIG. 1).

15

### Example 2

## MATERIALS AND METHODS

### Animals

Male Sprague Dawley rats (250-300g), obtained from Charles River, Margate, U.K.) were housed in groups of 3-6. All animals were kept under a 12h light/dark cycle (lights on at 07h 00min) with food and water *ad libitum*. All experiments were carried out by an observer blind to drug treatments.

Diabetes was induced in rats by a single i.p. injection of streptozocin (50mg/kg) as described previously (Courteix et al., 1993).

25

### Development of Chronic Constriction Injury in the rat

Animals were anaesthetised with 2% isoflurane 1:4 O<sub>2</sub>/N<sub>2</sub>O mixture maintained during surgery via a nose cone. The sciatic nerve was ligated as previously described by Bennett and Xie, 1988. Animals were placed on a homeothermic blanket for the duration of the procedure. After surgical preparation the common sciatic nerve was exposed at the middle of the thigh

30

by blunt dissection through biceps femoris. Proximal to the sciatic trifurcation, about 7mm of nerve was freed of adhering tissue and 4 ligatures (4-0 silk) were tied loosely around it with about 1mm spacing. The incision was closed in layers and the wound treated with topical antibiotics.

5

#### Intrathecal injections

PD 198306 and pregabalin were administered intrathecally in a volume of 10  $\mu$ l using a 100  $\mu$ l Hamilton syringe by exposing the spine of the rats under brief isoflurane anaesthesia. Injections were made into the intrathecal space  
10 between lumbar region 5-6 with a 10 mm long 27 gauge needle. Penetrations were judged successful if there was a tail flick response. The wound was sealed with an autoclip and rats appeared fully awake within 2-3 min following injection.

#### Evaluation of static allodynia

15 Mechanical hypersensitivity was measured using Semmes-Weinstein von Frey hairs (Stoelting, Illinois, U.S.A.). Animals were placed into wire mesh bottom cages allowing access to the underside of their paws. Animals were habituated to this environment prior to the start of the experiment. Mechanical hypersensitivity was tested by touching the plantar surface of the animals right  
20 hind paw with von Frey hairs in ascending order of force ( 0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1 and 29g) for up to 6sec. Once a withdrawal response was established, the paw was re-tested, starting with the next descending von Frey hair until no response occurred. The highest force of 29g lifted the paw as well as eliciting a response, thus represented the cut off point. The lowest  
25 amount of force required to elicit a response was recorded as the paw withdrawal threshold (PWT) in grams.

#### Experimental protocol

Static allodynia was assessed with von Frey hairs, before (baseline,  
30 BL) and 0.5h, 1h and 2h after intrathecal or intraplantar administration of PD 198306 (1-30 $\mu$ g, i.t.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (10 $\mu$ g, i.t). For oral administration experiments, static allodynia was assessed

with von Frey hairs, before (baseline, BL) and 1h after oral administration of PD 198306 (3-30mg/kg, p.o.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (30mg/kg, p.o.). Animals were administered again the same compounds on the following day, both in the morning and the afternoon. Static allodynia was assessed before and 1h after the morning administration. In the afternoon static allodynia was assessed before, 1h, 2h and 3h after administration for streptozocin treated animals. CCI animals were assessed before, 1h and 2h after administration

#### 10 Drugs used

PD 198306 and pregabalin were synthesised at Parke-Davis (Ann Arbor, MI, USA). PD 198306 was suspended in cremophor:ethanol:water (1:1:8) vehicle. Pregabalin was dissolved in water. Both compounds were administered orally, intrathecally or intraplantar in volumes of 1ml/kg, 10µl and 15 100µl respectively. Streptozocin (Aldrich, UK) was dissolved in 0.9% w/v NaCl and administered intraperitoneally in a volume of 1ml/kg.

#### Statistics

Data were analysed using a Kruskal-Wallis ANOVA for non-parametric results, followed when significant by Mann-Whitney's t test vs vehicle group. 20

## RESULTS

### **1. Effects of PD 198306 on static allodynia, following systemic administration**

#### 25 1.1. Effect of PD198306 on streptozocin-induced static allodynia

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked streptozocin-induced static allodynia 1h after administration. In contrast, a single administration of PD 198306 (3-30mg/kg, p.o) had no effect on streptozocin-induced static allodynia 1h after administration (FIG. 2).

30 However, after the compound had been administered twice more on the following day, PD 198306 (30mg/kg) significantly blocked streptozocin-induced static allodynia for 2h after the third administration (FIG. 2).

### 1.2. Effect of PD198306 on CCI-induced static allodynia

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked CCI-induced static allodynia 1h after administration. In contrast, neither a single or  
5 multiple administration of PD 198306 (3-30mg/kg, p.o) had any effect on CCI-induced static allodynia (FIG. 3).

### **2. Effects of PD 198306 on static allodynia, following intrathecal administration**

10 Intrathecally administered PD198306 (1-30 $\mu$ g) dose-dependently blocked the maintenance of static allodynia in both streptozocin (FIG. 4) and CCI animals (FIG. 5) with respective MEDs of 3 and 10  $\mu$ g. This antiallodynic effect lasted for 1h.

### **3. Effects of PD 198306 on static allodynia, following intraplantar administration**

An intrathecal administration of PD 198306 (30 $\mu$ g) significantly blocked static allodynia in both neuropathic pain models (FIGS. 6,7). In contrast, a single  
20 administration of PD 198306 at a dose 100-fold higher (3mg/100 $\mu$ l) directly into the paw had no effect on streptozocin (FIG. 6) or CCI-induced static allodynia (FIG. 7).

### REFERENCES

Bennett GJ, Xie Y-K. A peripheral mononeuropathy in rat that produces  
25 disorders of pain sensation like those seen in man. Pain 1988;33:87-107.

Courteix C, Eschalier A and Lavarenne J. Streptozocin –induced rats: behavioural evidence for a model of chronic pain. Pain 1993;53:81-8

### Example 3

#### Effect of other MEK inhibitors in a neuropathic pain model in the rat

##### 5 SUMMARY

The effect of several MEK inhibitors, with different binding affinities, has been investigated in the CCI model of neuropathic pain in the rat, by assessing static allodynia with von Frey hairs. Intrathecal administration of PD219622 or PD297447 (30µg) had no significant effect on allodynia. This lack of effect  
 10 may reflect the low affinity or solubility of the compounds. However, intrathecal administration of PD 254552 or PD 184352 (30µg), which possesses higher binding affinities, blocked the maintenance of static allodynia in CCI animals. The antiallodynic effect was only evident for 30min post-injection and thus, shorter than the one observed for pregabalin (100µg). The magnitude of  
 15 the effect was similar for 30µg of PD 184352 and 100µg of pregabalin. From this study it is concluded that MEK inhibitors exert an antiallodynic effect in CCI-induced neuropathic rats when administered intrathecally, and that the antiallodynic effect correlates with the affinity of the compounds.

20 The animals and methods for developing chronic constriction injury in the rat, injecting test compounds, and evaluation of static allodynia were according to Example 2 above. PD219622, PD297447, PD 184352, PD 254552 and pregabalin were administered intrathecally at doses of 30µg for all PD compounds and 100µg for pregabalin. Static allodynia was assessed with  
 25 von Frey hairs, before (baseline, BL) and 0.5h, 1h and 2h after intrathecal administration of the compounds

##### Drugs used

PD297447, PD219622, PD 254552, PD 184352 (CI-1040), and pregabalin  
 30 were synthesised at Parke-Davis (Ann Arbor, MI, USA). PD297447, PD219622, PD 254552 and PD 184352 were suspended in





# CHEMICAL EXAMPLES

## EXAMPLE 1

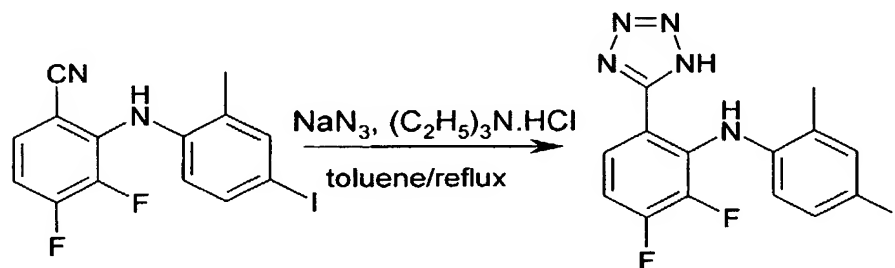
5 [4-Chloro-2-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine (18). (Scheme 2, R<sub>1</sub>=Cl, R<sub>2</sub>=R<sub>3</sub>=H, R<sub>4</sub>=CH<sub>3</sub>)

a). A mixture of 5-chloro-2-methoxybenzoic acid 16 (14.8 g, 0.0793 mole) and SOCl<sub>2</sub> (28.31 g, 14.97 ml, 0.1584 mole) was refluxed for 2 hours and  
10 excess SOCl<sub>2</sub> removed leaving a white residue. The solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and added to a solution of 2-amino-2-methyl-1-propanol (13.98 g, 14.97 ml, 0.1584 mole) in CH<sub>2</sub>Cl<sub>2</sub> cooled with ice-bath. The ice-bath was removed, and after stirring at room temperature for 3 hours a white solid precipitated. The precipitate was separated by filtration and discarded. The  
15 filtrate was concentrated leaving a thick colorless oil. SOCl<sub>2</sub> (17.4 ml) was added to the oil dropwise. An exothermic reaction took place resulting in to a freely flowing solution. After stirring for 30 minutes, the reaction mixture was poured in to Et<sub>2</sub>O (200 ml). An oil separated out. The Et<sub>2</sub>O layer was removed by decanting and discarded. The oily residue was dissolved in a  
20 minimum amount of water, basified with aqueous 20% NaOH, and extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O layer was dried (K<sub>2</sub>CO<sub>3</sub>) and concentrated to give **17** as tan oil. Yield 14.63 g (77%).

b). LDA (5 ml of 2.0 M solution in THF) was added to a solution of 4-iodo-  
25 2-methylaniline (2.33 g, 0.010 mole) in THF (15 ml) at -78 °C. The mixture was stirred at -78 °C for 30 minutes. To this, a solution of **17** (1.199 g, 0.005 mole) in THF (15 ml) was added. The mixture stirred for 16 hours as it warmed up to room temperature. The reaction mixture was quenched with aqueous NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O layer was dried (MgSO<sub>4</sub>)  
30 and concentrated to give crude **18** as brown oil. The oil was purified on silica column chromatography. Eluting with CH<sub>2</sub>Cl<sub>2</sub> gave pure 1.7 g (77%) of **18** as brown oil. Four hundred and nine milligrams of the oil were dissolved in Et<sub>2</sub>O and treated with Et<sub>2</sub>O-HCl giving the HCl salt as a light yellow solid

precipitate. Yield 356.4 mg (81%); mp 324-330 °C; Anal. Calcd/found for  $C_{18}H_{18}N_2OCl \cdot HCl \cdot 0.5H_2O$ : C, 44.47/44.32; H, 4.15/3.94; N, 5.76/5.66.

## EXAMPLE 2

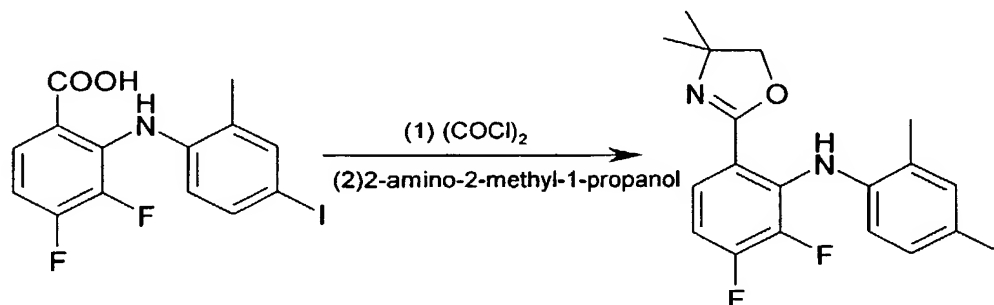
[2,3-Difluoro-6-(1*H*-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine

- 10        [2,3-Difluoro-6-cyano-phenyl]-(4-iodo-2-methyl-phenyl)-amine (1.11g, 3mmol) and Sodium azide(0.255g, 3.9mmol) and triethylamine hydrochloride (0.537g, 3.9mmol) were all suspended in 10ml toluene and stirred at 100°C for 12 hours. The mixture was concentrated and the residue purified by column chromatography with ethyl acetate/methanol (10/1) to give the product
- 15        as a foam-like solid. The yield: ~50%  
           m.p: 83.4-88.7°C  
            $^1H$  NMR( $CDCl_3$ , 400Hz):  $\delta$ /ppm 7.69(1H, m, Phenyl-H); 7.42(1H, s, Phenyl-H); 7.27(1H, m, Phenyl-H); 6.91(1H, dd,  $J=16.2Hz$ , 8.3Hz, Phenyl-H); 6.40(1H, dd, Phenyl-H); 2.28(3H, s,  $CH_3$ )

20

### EXAMPLE 3

#### [6-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine



5

A solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (1.17g, 3mmol), oxalyl chloride (0.457g, 3.6mmol) in 30ml dichloromethane was treated with 2 drops of dimethylformamide, stirred at room temperature for 3 hours then concentrated. The residue was dissolved in 25 ml dichloromethane then the solution was added dropwise to a solution of 2 amino-2-methyl-1-propanol (0.623g, 7mmol) in 25 ml dichloromethane at 0°C, then stirred at room temperature for 12 hours, filtered off the precipitate, the filtration was washed with water, 5% aqueous sodium bicarbonate, 1 N HCl, brine, dried with sodium sulfate. Concentration gave the crude product, then resuspended in 25 ml chloroform, then thionyl chloride was added at 0°C and stirred at room temperature for 15 hours, then concentrated and the residue was dissolved in 30 ml dichloromethane, 1 N HCl was added to adjusted the pH value to 11, the separated and extracted with chloroform, dried with sodium sulfate. Concentrated and then run column with hexanes/dichloromethane (20/1) to give the compound as a white crystal. The yield: 65%

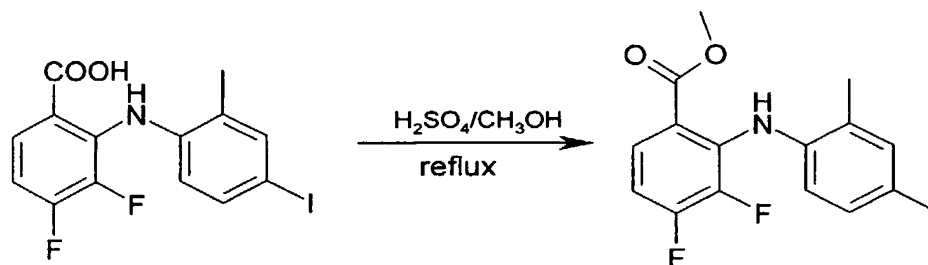
m.p.: 103.7-104.4°C

<sup>1</sup>H NMR(CDCl<sub>3</sub>, 400Hz): δ/ppm 10.2(1H, s, NH), 7.48-7.58(1H, m, Phenyl-H); 7.48(1H, s, Phenyl-H); 7.38(1H, d, J=8.5Hz, Phenyl-H), 6.66-6.72(1H, m, Phenyl-H); 6.58(1H, t, J=8.0Hz, Phenyl-H); 4.01(2H, s, -CH<sub>2</sub>-); 2.31(3H, s, Phenyl-CH<sub>3</sub>); 1.32(6H, s, -C(CH<sub>3</sub>)<sub>2</sub>-)

25

EXAMPLE 4

5 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid methyl ester



10 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (5g) was dissolved in 100ml methanol and 5 drops of concentrated sulfuric acid was added, reflux for 4 days. Run column with hexanes/dichloromethane to give the product as a white solid, yield: 50%.

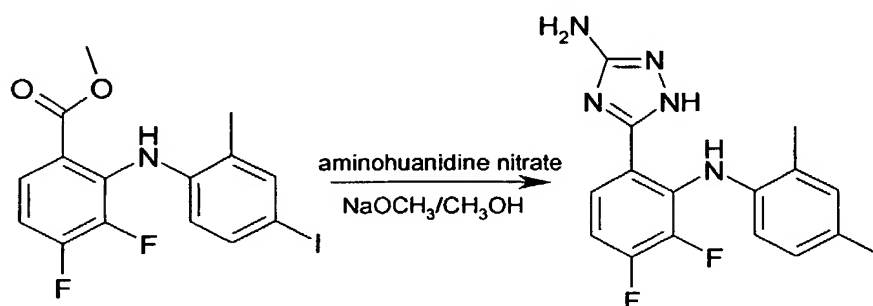
m.p.:90.1-90.4°C

15 <sup>1</sup>H NMR(CDCl<sub>3</sub>, 400Hz): δ/ppm 8.92(1H, s, NH), 7.75-7.78(1H, m, Phenyl-H); 7.49(1H, s, Phenyl-H); 7.38(1H, dd, J=8.5Hz, 2.0Hz, Phenyl-H), 6.66-6.73(1H, m, Phenyl-H); 6.56-6.60(1H, m, Phenyl-H); 3.88(3H, s, -OCH<sub>3</sub>); 2.30(3H, s, Phenyl-CH<sub>3</sub>)

EXAMPLE 5

5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine

5



Aminoguanidine nitrate (1.65g, 12mmol) was added to a solution of sodium methoxide (0.648g, 12mmol) in methanol (12ml) at 0°C, then 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid methyl ester was added as a solution of methanol and reflux for 20 hours, concentration and run column with hexanes/ethyl acetate to give the product as a white crystal. The yield: 60%

m.p.: 191.7-192.0°C

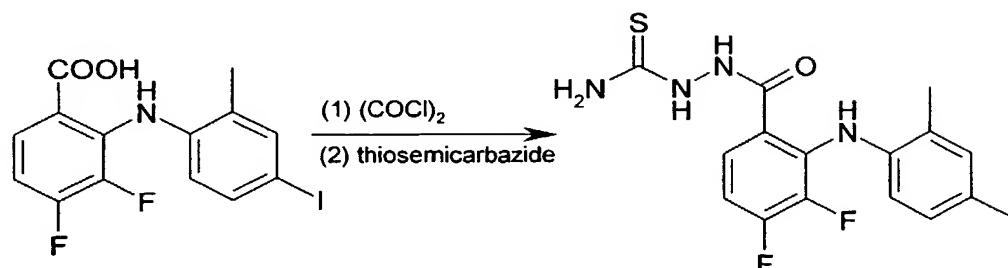
<sup>1</sup>H NMR(DMSO, 400Hz): δ/ppm 9.45(1H, s, -NH-); 7.79(1H, t, J=7.3Hz, Phenyl-H); 7.51(1H, s, Phenyl-H); 7.35(1H, d, J=10.1Hz, Phenyl-H); 7.05-7.11(1H, m, Phenyl-H); 6.44-6.48(1H, m, Phenyl-H); 6.32(2H, s, -NH<sub>2</sub>), 2.32(3H, s, CH<sub>3</sub>)



## EXAMPLE 7

2-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-  
benzoyl]hydrazinecarbothioamide

5



A solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (3.9g, 0.01mol), oxalyl chloride (1.90g, 0.015mol) in 40ml dichloromethane was treated with 2 drops of dimethylformamide, stirred at room temperature for 3 hours before concentration. The residue was dissolved in 10 ml tetrahydrofuran and added to a solution of thiosemicarbazide (2.0g, 0.022mol) in 50ml tetrahydrofuran at 0°C, stirred at room temperature for 14 hours. Concentrated and run column chromatography with hexanes/ethyl acetate (1/1) to give the product as a yellow solid. 2.91g. The yield: 63%

15 m.p.: 159.5-160.0°C

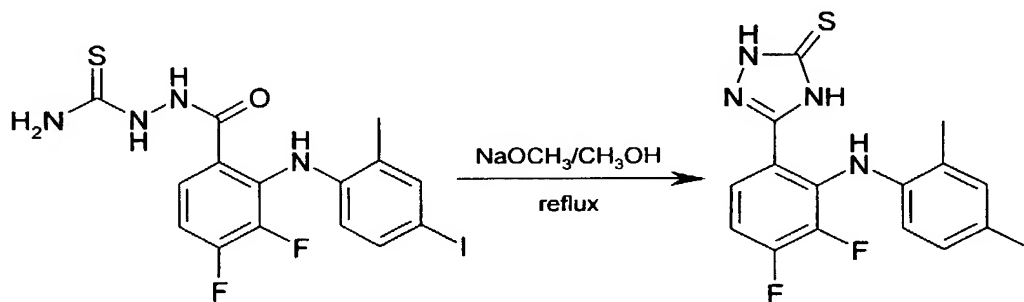
<sup>1</sup>H NMR(DMSO, 400Hz): δ/ppm 10.58(1H, s, -NH-); 9.28(1H, s, -NH-); 8.83(1H, s, -NH-); 7.95(1H, s, Phenyl-H); 7.12-7.75(2H, m, NH<sub>2</sub>); 7.51(1H, s, Phenyl-H); 7.37(1H, dd, J=8.6Hz, 1.7Hz, Phenyl-H); 7.16(1H, dd, J=17Hz, 9.0Hz, Phenyl-H); 6.40-6.50(1H, m, Phenyl-H); 5.02(2H, s, -NH<sub>2</sub>), 2.00(3H, s, CH<sub>3</sub>)



## EXAMPLE 8

5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol

5



2-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-

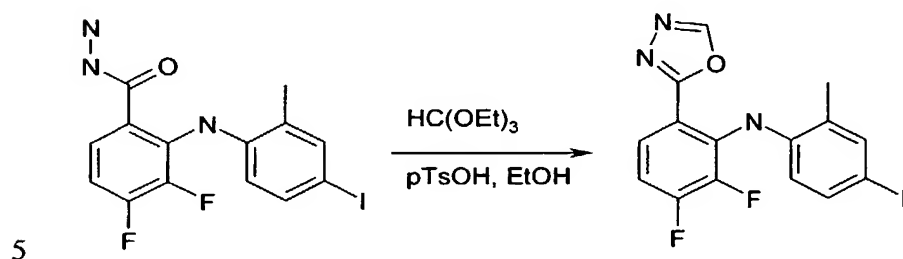
10 benzoyl]hydrazinecarbothioamide (1.386g, 3mmol) was dissolved in 15 ml anhydrous methanol, sodium methoxide (25% wt% in methanol) 2.5ml was added at 0°C in one portion. The resulting mixture was heated at reflux for 17 hours before concentration. Run column with hexanes/ethyl acetate to give the product as a needle white crystal. The yield: 40%

m.p.: 196.5(dec.)

15 <sup>1</sup>H NMR(DMSO, 400Hz): δ/ppm 13.87(1H, s, -NH-); 13.80(1H, s, -NH-); 8.16(1H, s, -NH-); 7.61-7.65(1H, m, Phenyl-H); 7.48(1H, s, Phenyl-H); 7.32(1H, dd, J=8.6Hz, 2.2Hz, Phenyl-H); 7.24(1H, dd, J=16.4Hz, 9.5Hz, Phenyl-H); 6.42-6.46(1H, m, Phenyl-H); 5.02(2H, s, -NH<sub>2</sub>), 2.20(3H, s, CH<sub>3</sub>).

# EXAMPLE 9

## (2,3-Difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)-(4-iodo-2-methyl-phenyl)-amine



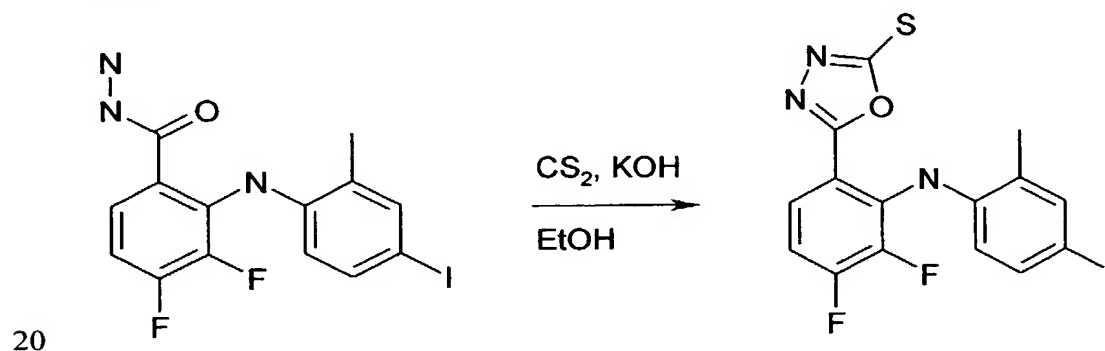
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (146 mg, 0.36 mmol) was suspended in 7 mL of absolute EtOH and 2 mL of HC(OEt)<sub>3</sub> was added along with approximately 3 mg of pTsOH. The reaction was heated to reflux for 3h, cooled and concentration on a rotary evaporator. The reaction was purified (SiO<sub>2</sub>, 4:1 Hexane/EtOAc) to afford 117 mg (79%) of (2,3-difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)-(4-iodo-2-methyl-phenyl)-amine as a yellow powder. M.p. = 144.4 – 145.5 °C. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 8.89 (s, 1H), 8.44 (s, 1H), 7.66 (m, 1H), 7.52 (d, J = 1.7 Hz, 1 H), 7.38 (dd, J = 8.5, 1.9 Hz, 1 H), 6.83 (m, 1H), 6.14 (dd, J = 8.5, 5.9 Hz, 1 H), 2.37 (s, 3 H).

10

15

# EXAMPLE 10

## 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol



3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (170 mg, 0.42 mmol) was suspended in 7 mL of absolute EtOH and cooled to

0 °C. Carbon disulfide (74 mg, 0.97 mmol) was added followed by 24 mg  
(0.42 mmol) of powdered KOH. The reaction was stirred for 1 h at 0 °C, 1h at  
rt, and refluxed for 3 h to afford a homogeneous reaction. The reaction was  
5 diluted with 5 mL of EtOAc. 1N HCl was added to acidify the aqueous layer  
(pH = 2). The aqueous layer was extracted with EtOAc (3x). The combined  
organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to obtain 96 mg  
(51%) of 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-  
[1,3,4]oxadiazole-2-thiol as a yellow powder. M.p. = 231.8 – 232.8 °C. <sup>1</sup>H  
10 NMR (400MHz, CDCl<sub>3</sub>) δ 7.62 (m, 2H), 7.47 (s, 1H), 7.30 (complex m, 2H),  
6.44 (dd, J = 8.0, 4.5 Hz, 1H), 2.19 (s, 3H).

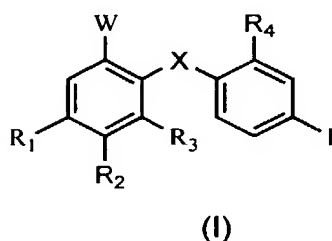
#### F. OTHER EMBODIMENTS

From the above disclosure and examples, and from the claims below,  
the essential features of the invention are readily apparent. The scope of the  
15 invention also encompasses various modifications and adaptations within the  
knowledge of a person of ordinary skill. Examples include a disclosed  
compound modified by addition or removal of a protecting group, or an ester,  
pharmaceutical salt, hydrate, acid, or amide of a disclosed compound.  
Publications cited herein are hereby incorporated by reference in their  
20 entirety.

What is claimed is:

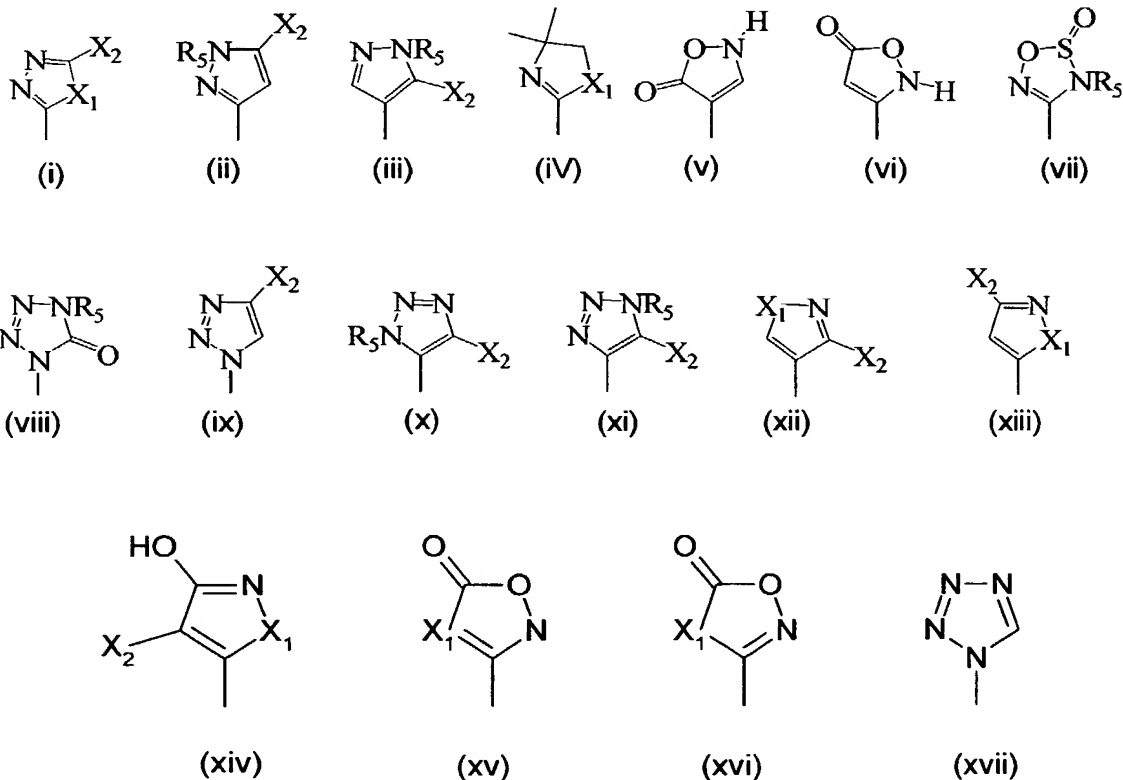
# CLAIMS

1. A method for treating chronic pain, said method comprising administering to a subject in need of such treatment a composition comprising
- 5 a MEK inhibitor selected from: a compound of formula (I):



10

W is one of the following formulae (i) – (xiii):



15

X<sub>1</sub> is O, S, or NR<sub>F</sub>;

$X_2$  is OH, SH, or  $NHR_E$ ;

each of  $R_E$  and  $R_F$  is H or  $C_{1-4}$  alkyl;

5

each of  $R_1$  and  $R_2$  is independently selected from H, F,  $NO_2$ , Br and Cl;  
 $R_1$  can also be  $SO_2NR_GR_H$ , or  $R_1$  and  $R_2$  together with the benzene ring to  
 which they are attached constitute an indole, isoindole, benzofuran,  
 benzothiophene, indazole, benzimidazole, or benzthioazole;

10

$R_3$  is H or F;

each of  $R_G$ ,  $R_H$ , and  $R_4$  is independently selected from H, Cl and  $CH_3$ ;

15

$R_5$  is H or  $C_{3-4}$  alkyl; and

wherein each hydrocarbon radical above is optionally substituted with  
 between 1 and 3 substituents independently selected from halo, hydroxyl,  
 amino, (amino)sulfonyl, and  $NO_2$ ; and

20

wherein each heterocyclic radical above is optionally substituted with between  
 1 and 3 substituents independently selected from halo,  $C_{3-4}$  alkyl,  $C_{3-6}$   
 cycloalkyl,  $C_{3-4}$  alkenyl,  $C_{3-4}$  alkynyl, phenyl, hydroxyl, amino,  
 (amino)sulfonyl, and  $NO_2$ , wherein each substituent alkyl, cycloalkyl, alkenyl,  
 25 alkynyl or phenyl is in turn optionally substituted with between 1 and 2  
 substituents independently selected from halo,  $C_{1-2}$  alkyl, hydroxyl, amino,  
 and  $NO_2$ ;

25

or a pharmaceutically acceptable salt or  $C_{1-8}$  ester thereof.

30



- 89

27. A method of claim 1, wherein said MEK inhibitor has a structure selected from: [5-fluoro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; (4-iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(1H-tetrazol-5-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3,4-trifluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [4-bromo-6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-4-nitro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ol.



28. A method of claim 1, wherein said MEK inhibitor has a structure selected from: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4,5-

trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazole-3-thiol.

5

29. A method of claim 1, wherein said MEK inhibitor has a structure selected from: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-

methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1-methyl-1H-pyrazol-3-ol.

30. A method of claim 1, wherein said MEK inhibitor has a structure selected from: 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4,5-trifluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-5-bromo-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-5-nitro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 3-methyl-5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3H-[1,2,3]triazol-4-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 2-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2-methyl-2H-pyrazol-3-ol; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1,4-dihydro-tetrazol-5-one; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-

1H-[1,2,3]triazol-4-ol; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-  
 1H-[1,2,3]triazol-4-ol; 1-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-  
 phenyl]-1H-[1,2,3]triazol-4-ol; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-  
 phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; and 1-[4-fluoro-2-(4-iodo-2-  
 5 methyl-phenylamino)-5-nitro-phenyl]-1H-[1,2,3]triazol-4-ol.

31. The method of claim 1, wherein said MEK inhibitor has a structure  
 selected from: 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-  
 isoxazol-5-one; 3-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-  
 10 isoxazol-5-one; 3-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-  
 isoxazol-5-one; 3-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-  
 phenyl]-2H-isoxazol-5-one; 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-  
 nitro-phenyl]-2H-isoxazol-5-one; [5-fluoro-2-(2-oxo-2,3-dihydro-2l>4\_-  
 [1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-  
 15 difluoro-6-(2-oxo-2,3-dihydro-2l>4\_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-  
 iodo-2-methyl-phenyl)-amine; (4-iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(2-  
 oxo-2,3-dihydro-2l>4\_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-amine; [4-bromo-  
 2,3-difluoro-6-(2-oxo-2,3-dihydro-2l>4\_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-  
 iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(2-oxo-2,3-dihydro-2l>4\_-  
 20 [1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; 4-[4-  
 fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4-  
 difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4,5-  
 trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[5-  
 bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-  
 25 one; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-  
 isoxazol-5-one.

32. The method of claim 1, wherein said MEK inhibitor has a structure  
 selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3fluoro5-nitro-benzoic  
 30 acid; 5-[3,4difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-  
 2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-  
 [1,3,4]oxadiazol-2-ol; (2,3-difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)-(4-iodo-2-

methyl-phenyl)-amine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazole-3-ylamine; and 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazole-3-thiol.

5

33. The method of claim 1, wherein said MEK inhibitor has the structure: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number  
**WO 01/05391 A3**

(51) International Patent Classification?: **A61K 31/41**,  
31/4245, 31/42, 31/433, 31/4196, 31/425, A61P 25/04

CB1 9YT (GB). ZHANG, Lu-Yan [CN/US]; 2411 Stone  
Road, Ann Arbor, MI 48105 (US).

(21) International Application Number: PCT/US00/18346

(74) Agents: RYAN, M., Andrea; Warner-Lambert Company,  
201 Tabor Road, Morris Plains, NJ 07950 et al. (US).

(22) International Filing Date: 5 July 2000 (05.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(81) Designated States (*national*): AE, AG, AL, AU, BA, BB,  
BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE,  
HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV,  
MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI,  
SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.

(30) Priority Data:  
60/144,403 16 July 1999 (16.07.1999) US

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*):  
**WARNER-LAMBERT COMPANY** [US/US]; 201  
Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BARRETT**,  
Stephen, Douglas [US/US]; 14220 Sunbury, Livonia, MI  
48154 (US). **BRIDGES**, Alexander, James [GB/US];  
3301 Textile Road, Saline, MI 48176 (US). **TECLE**, Haile  
[US/US]; 3048 Turnberry, Ann Arbor, MI 48108 (US).  
**DIXON**, Alistair [GB/GB]; 108 Gwydir Street, Cam-  
bridge CB1 2LL (GB). **LEE**, Kevin [GB/GB]; 81 Williams  
Smith Close, Cambridge CB1 9YT (GB). **PINNOCK**,  
Robert, Denham [GB/GB]; 3 Teasel Way, Cambridge

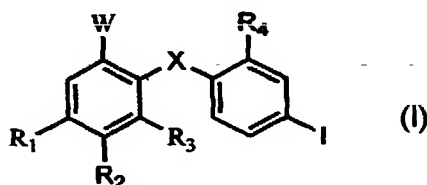
Published:

— with international search report

(88) Date of publication of the international search report:  
19 July 2001

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

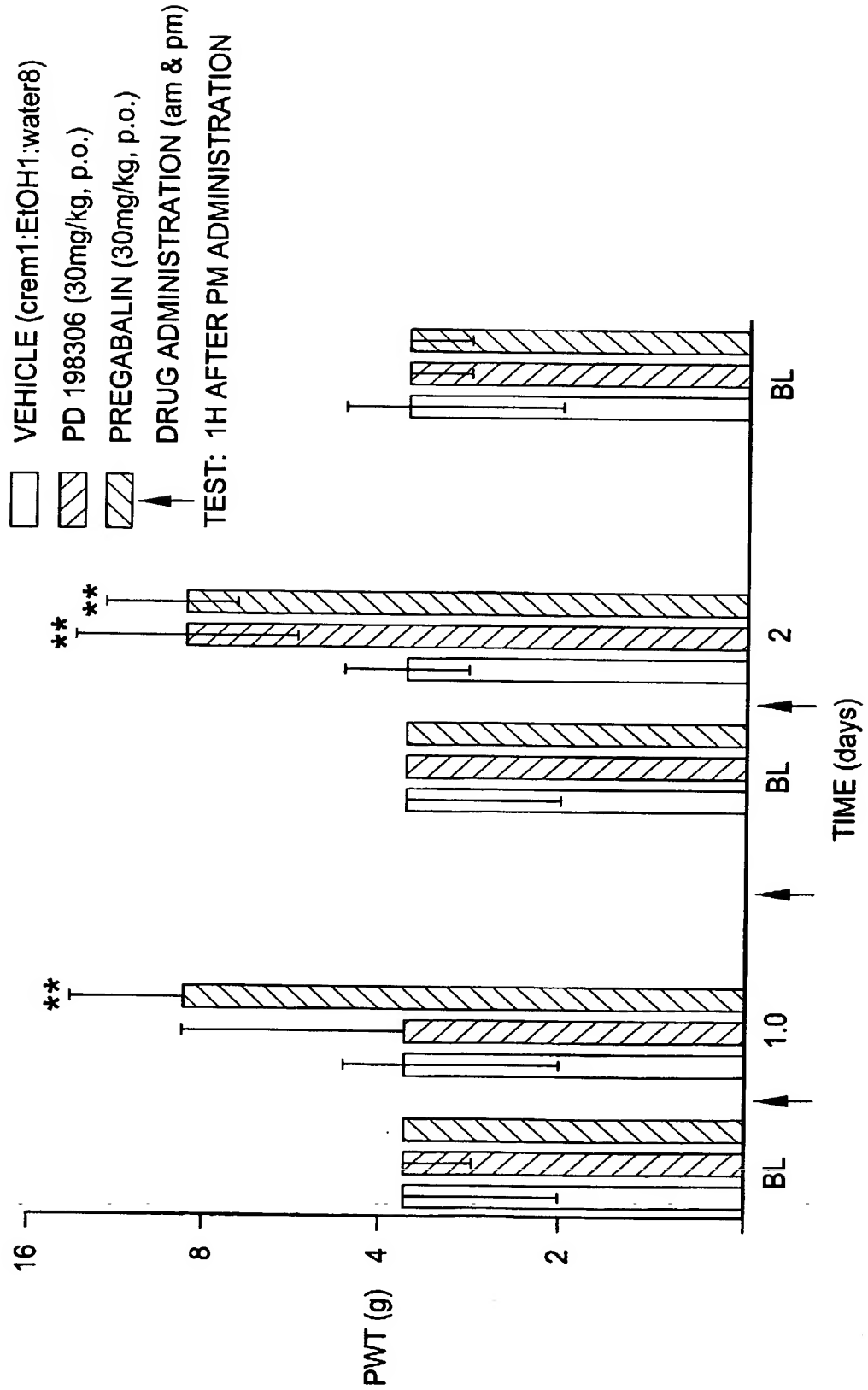
(54) Title: METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS



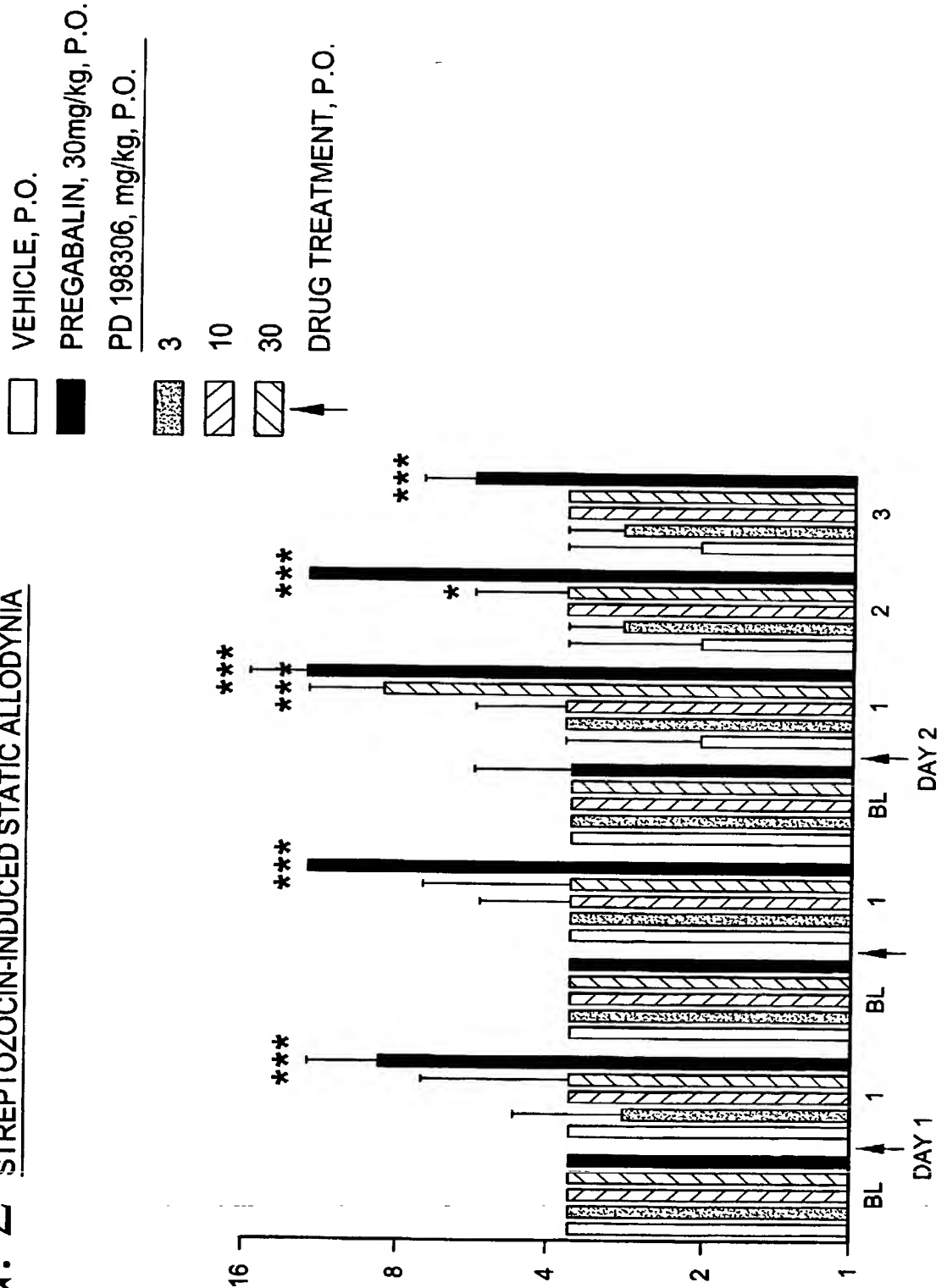
(57) Abstract: The invention features a method for treating chronic pain using the diarylamines disclosed in formula (I) of claim 1.

WO 01/05391 A3

**FIG. 1** EFFECT OF PD 198306 ON STREPTOZOCIN-INDUCED STATIC ALLODYNIA

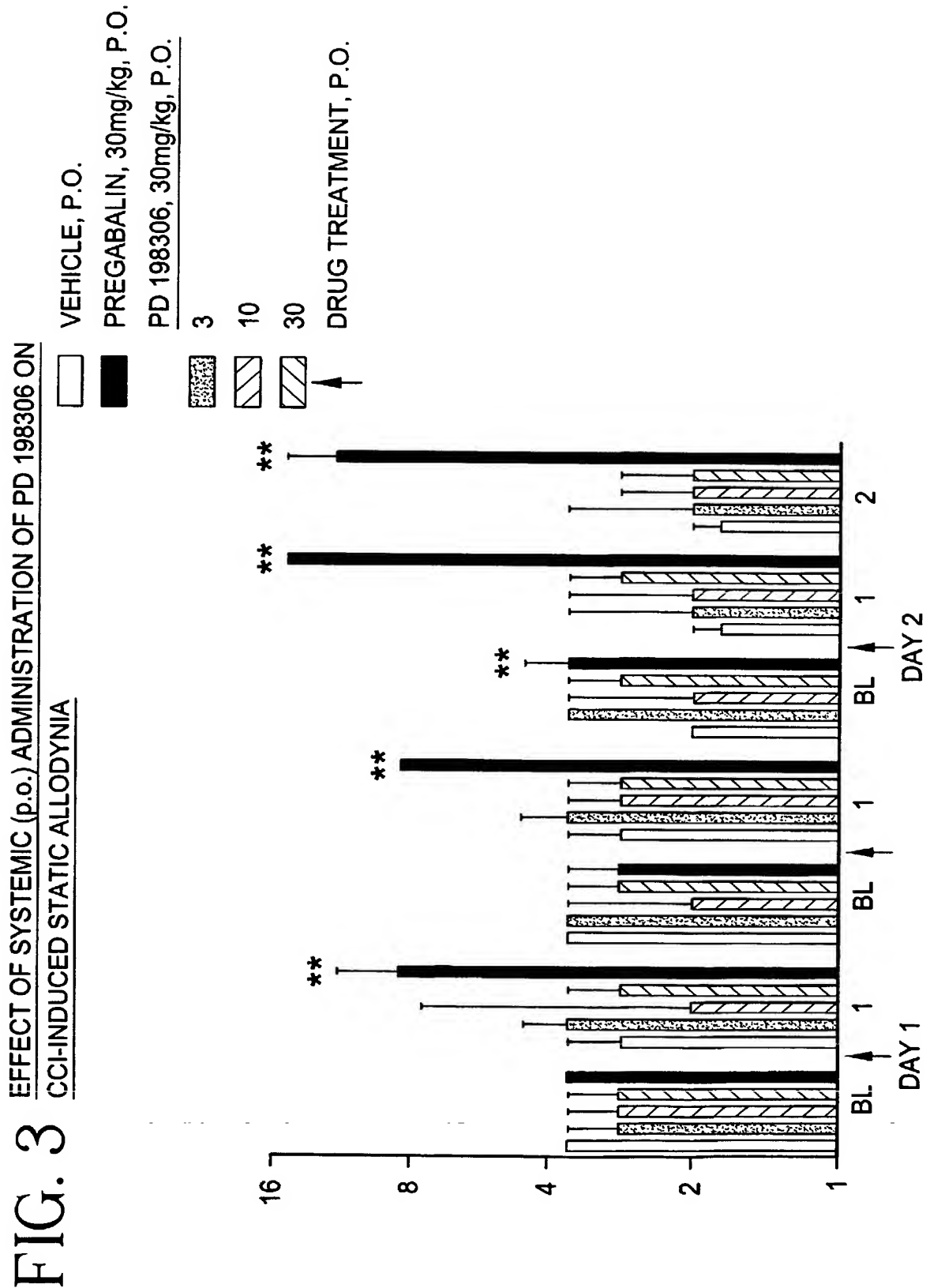


**FIG. 2**  
EFFECT OF SYSTEMIC (p.o.) ADMINISTRATION OF PD 198306 ON  
STREPTOZOCIN-INDUCED STATIC ALLODYNIA

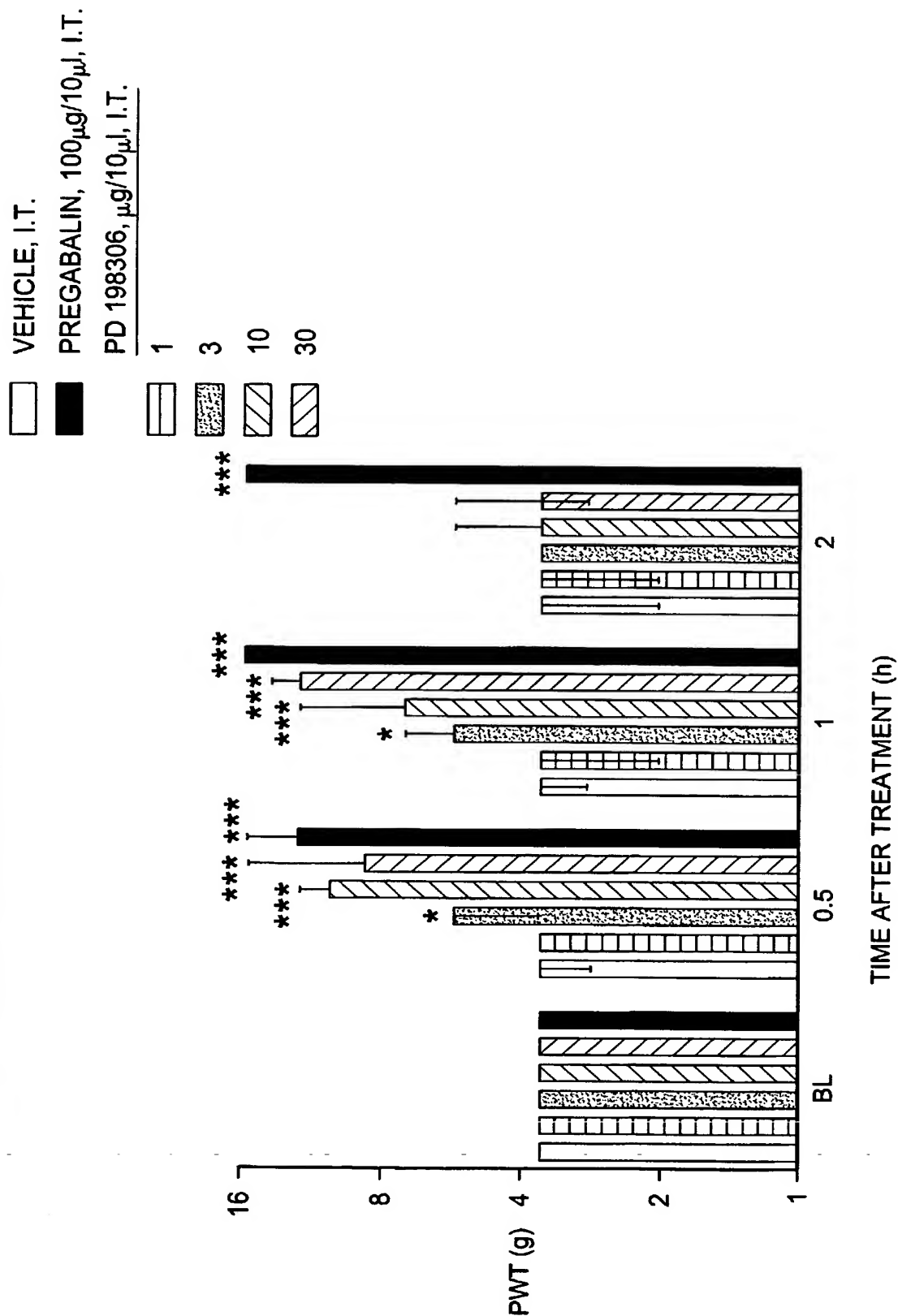


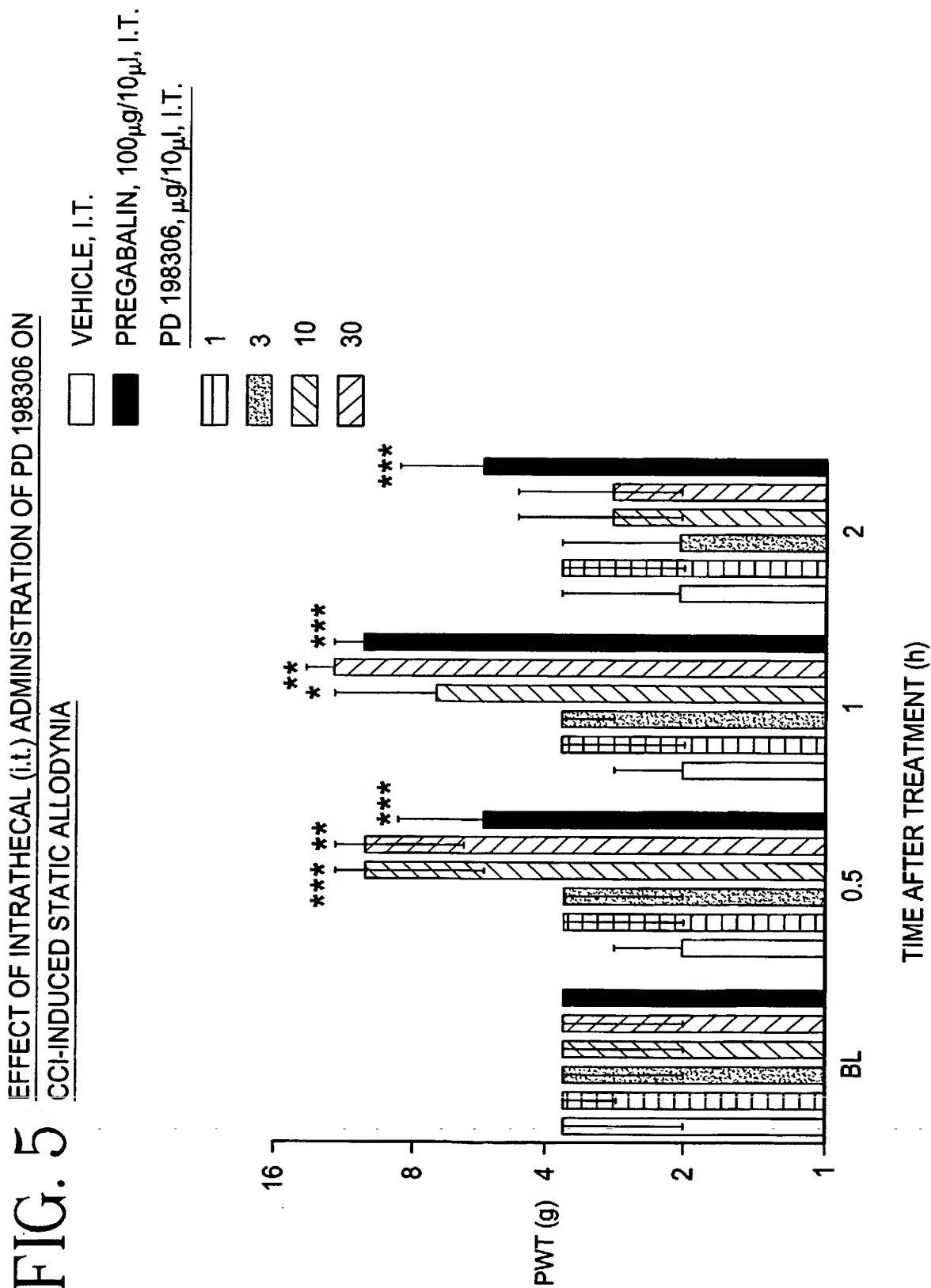


3/8



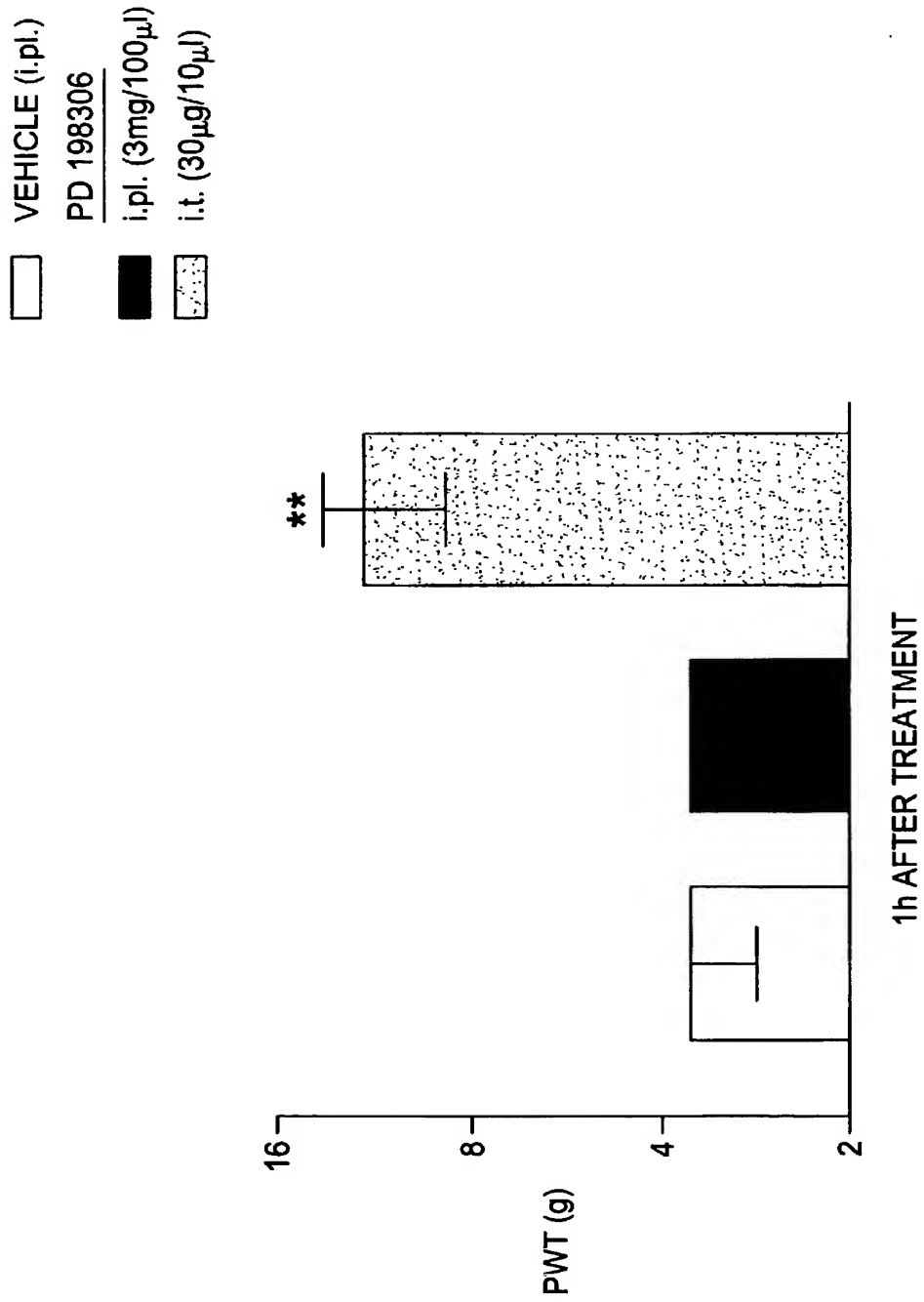
**FIG. 4** EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 198306 ON STREPTOZOCIN-INDUCED STATIC ALLODYNIA





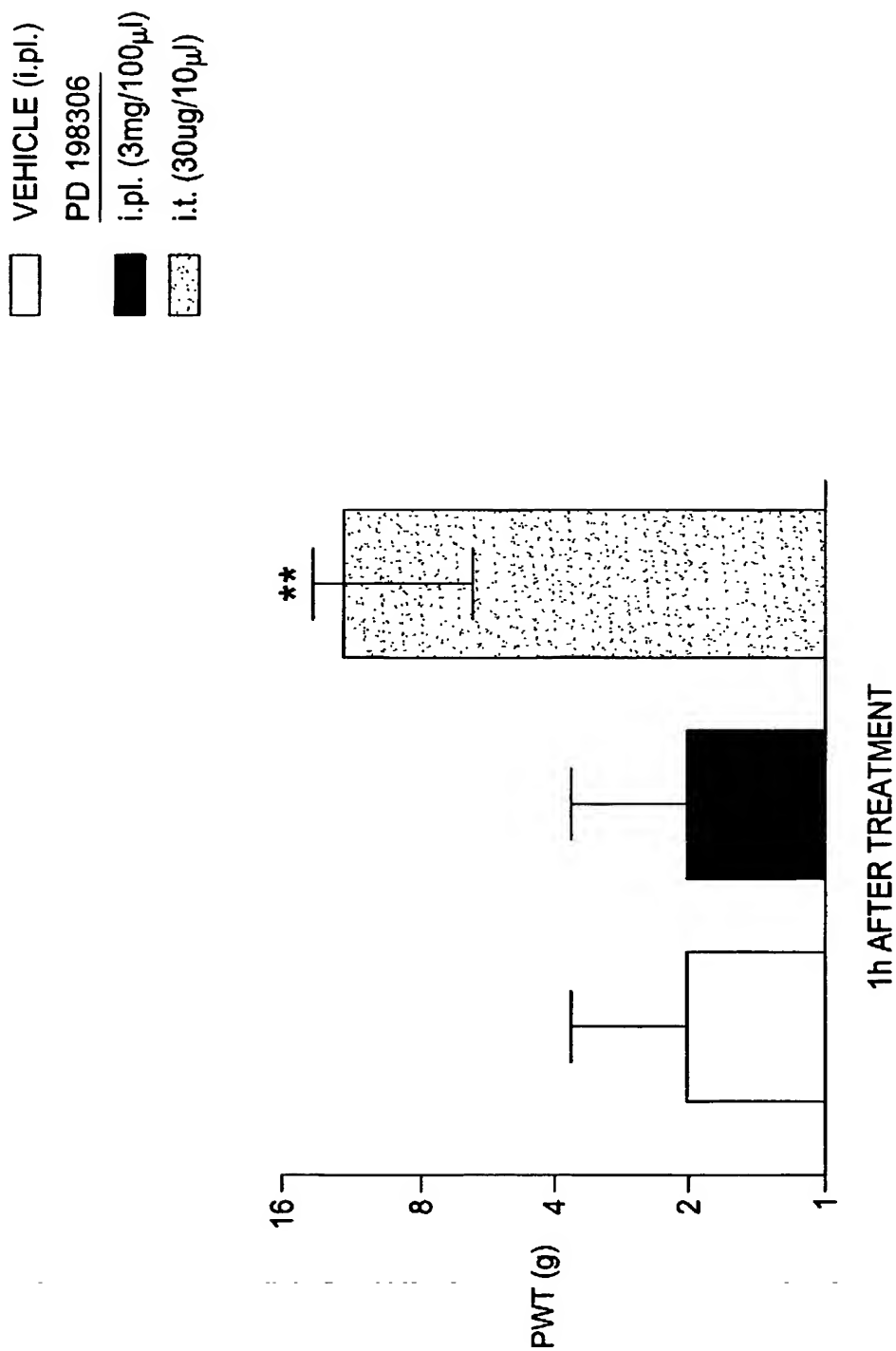
6/8

**FIG. 6**  
EFFECT OF INTRAPLANTAR (i.pl.) ADMINISTRATION OF PD 198306 ON  
STREPTOZOCIN-INDUCED STATIC ALLODYNIA

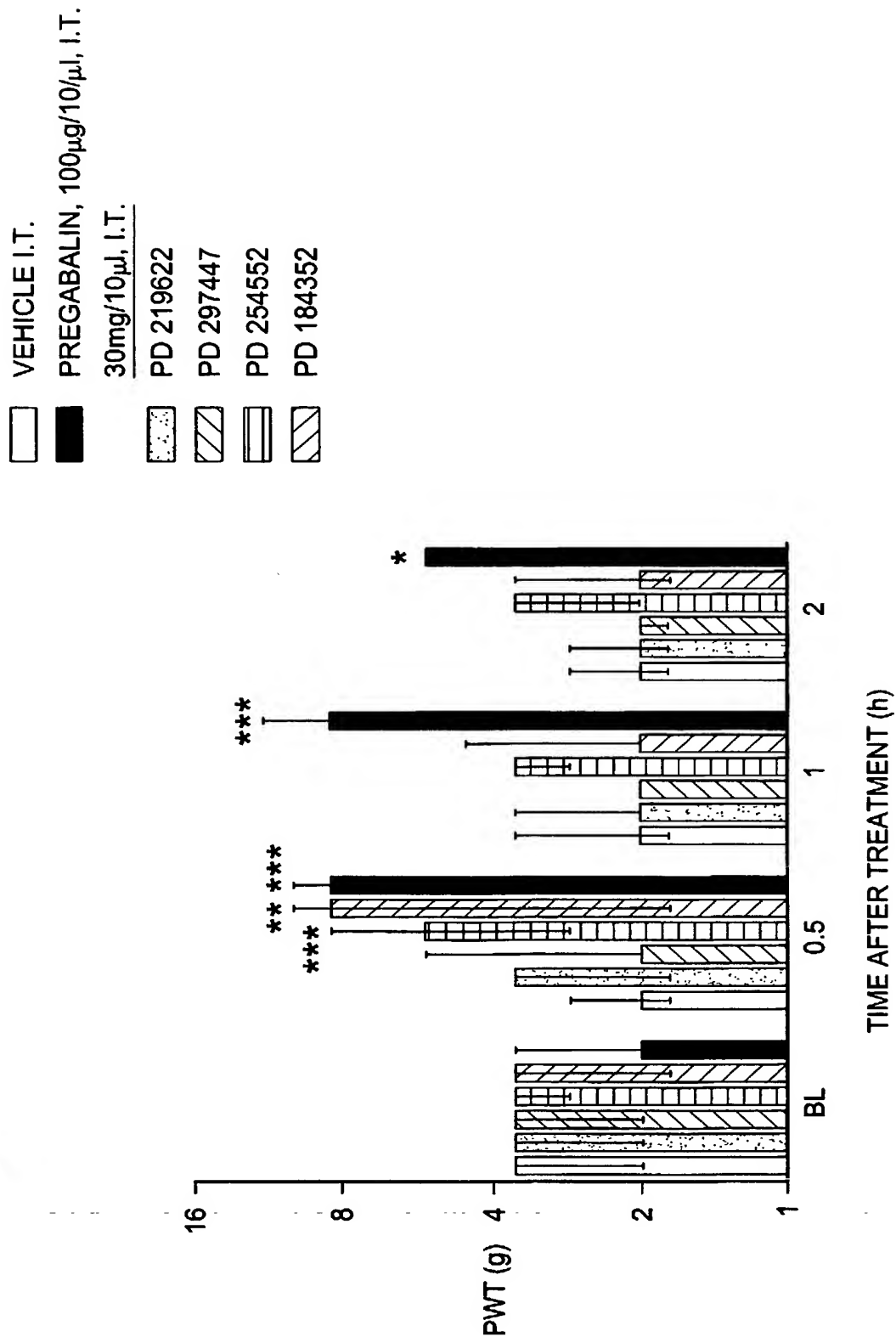


7/8

**FIG. 7** EFFECT OF INTRAPLANTAR (i.pl.) ADMINISTRATION OF PD 198306 ON CCI-INDUCED STATIC ALLODYNIA



**FIG. 8** EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 219622, PD 297447, PD 184352, PD 254552 OR PREGABALIN ON CCI-INDUCED STATIC ALLODYNIA



Docket No.  
A0000104-01-SMH

## Declaration and Power of Attorney For Patent Application

### English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on 05 July 2000 As United States Application No. \_\_\_\_\_ or PCT International  
Application Number PCT/US00/18346  
and was amended on \_\_\_\_\_  
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applications

Priority Not Claimed

(Number) (Country) (Day/Month/Year Filed)

☐

(Number) (Country) (Day/Month/Year Filed)

☐

(Number) (Country) (Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

<u>60/144,403</u>	<u>16 July 1999</u>
(Application Serial No.)	(Filing Date)

_____	_____
(Application Serial No.)	(Filing Date)

_____	_____
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

<u>PCT/US00/18346</u>	<u>05 July 2000</u>	<u>Pending</u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

_____	_____	_____
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

_____	_____	_____
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (*list name and registration number*)

Charles W. Ashbrook	<u>27,610</u>	Darryl C. Little	<u>40,703</u>
Heidi M. Berven	<u>48,951</u>	J. Trevor Lumb	<u>28,567</u>
Evan J. Federman	<u>37,060</u>	Claude F. Purchase, Jr.	<u>47,871</u>
Mehdi Ganjeizadeh	<u>47,585</u>	James Proscia	<u>47,010</u>
Rosanne Goodman	<u>32,534</u>	Francis J. Tinney	<u>33,069</u>
Suzanne M. Harvey	<u>42,640</u>	Linda Vag	<u>32,071</u>
David R. Kurlandsky	<u>41,505</u>		

Send Correspondence to: Suzanne M. Harvey  
Warner-Lambert Company  
2800 Plymouth Road  
Ann Arbor, Michigan 48105

Direct Telephone Calls to: (*name and telephone number*)  
Suzanne M. Harvey, (734) 622-2658

Full name of sole or first inventor	
<u>STEPHEN DOUGLAS BARRETT</u>	
Sole or first inventor signature	Date
<u>Stephen Douglas Barrett</u>	<u>11/13/01</u>
Residence	
<u>Livonia, Michigan 48154 United States M I</u>	
Citizenship	
<u>United States</u>	
Post Office Address	
<u>14220 Sunbury</u>	
<u>Livonia, Michigan 48154 United States</u>	

Full name of sole or second inventor	
<u>ALEXANDER JAMES BRIDGES</u>	
Sole or second inventor signature	Date
<u>Alexander J. Bridges</u>	<u>11/8/01</u>
Residence	
<u>Saline, Michigan 48176 United States M I</u>	
Citizenship	
<u>Great Britain</u>	
Post Office Address	
<u>3301 Textile Road</u>	
<u>Saline, Michigan 48176 United States</u>	

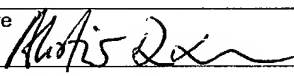
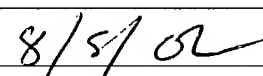
Full name of sole or third inventor	
<b>HAILE TECLE</b>	
Sole or third inventor signature	Date
<i>Haile Tecle</i>	11/07/07
Residence	
Ann Arbor, Michigan 48108 United States MI	
Citizenship	
United States	
Post Office Address	
3048 Turnberry	
Ann Arbor, Michigan 48108 United States	

Full name of sole or fourth inventor	
<b>ALISTAIR DIXON</b>	
Sole or fourth inventor signature	Date
SEE ATTACHED	
Residence	
Cambridge, UK CB1 2LL	
Citizenship	
Great Britain	
Post Office Address	
108 Gwydir Street	
Cambridge, UK CB1 2LL	

Full name of sole or fifth inventor	
<b>KEVIN LEE</b>	
Sole or fifth inventor signature	Date
<i>Kevin Lee</i>	23/02/01
Residence	
<del>Cambridge, UK CB1 3QE</del> <sup>KE</sup> Kenilworth, UK CV8 1D5 <sup>KE</sup> GBX	
Citizenship	
Great Britain	
Post Office Address	
<del>81 Williams Smith Close</del> <sup>KE</sup> 5 Archer Road <sup>KE</sup>	
<del>Cambridge, UK CB1 3QE</del> <sup>KE</sup> Kenilworth, UK, CV8 1D5 <sup>KE</sup>	

Full name of sole or sixth inventor	
<b>ROBERT PINNOCK</b>	
Sole or sixth inventor signature	Date
<i>Robert Pinnock</i>	18/12/07
Residence	
Cambridge, UK CB1 9YT GBX	
Citizenship	
Great Britain	
Post Office Address	
3 Teasel Way	
Cambridge, UK CB1 9YT	

Full name of sole or third inventor	
HAILE TECLE	
Sole or third inventor signature	Date
SEE PREVIOUS PAGE	
Residence	
Ann Arbor, Michigan 48108 United States	
Citizenship	
United States	
Post Office Address	
3048 Turnberry	
Ann Arbor, Michigan 48108 United States	

Full name of sole or fourth inventor	
ALISTAIR DIXON	
Sole or fourth inventor signature	Date
 	
Residence	
Cambridge, UK CB1 2LL GBX	
Citizenship	
Great Britain	
Post Office Address	
108 Gwydir Street	
Cambridge, UK CB1 2LL	

Full name of sole or fifth inventor	
KEVIN LEE	
Sole or fifth inventor signature	Date
SEE PREVIOUS PAGE	
Residence	
Cambridge, UK CB1 3QE	
Citizenship	
Great Britain	
Post Office Address	
81 Williams Smith Close	
Cambridge, UK CB1 3QE	

Full name of sole or sixth inventor	
ROBERT PINNOCK	
Sole or sixth inventor signature	Date
SEE PREVIOUS PAGE	
Residence	
Cambridge, UK CB1 9YT	
Citizenship	
Great Britain	
Post Office Address	
3 Teasel Way	
Cambridge, UK CB1 9YT	

7-00  
Full name of sole or third inventor

LU-YAN ZHANG

Sole or third inventor signature

*Lu-Yan Zhang*

Date

05/20/2002

Residence

Branford, CT 06405

Citizenship

China P.R.

Post Office Address

4 Brushy Plains Road, Apt. 219

Branford, CT 06405

Full name of sole or fourth inventor

Sole or fourth inventor signature

Date

Residence

Citizenship

Post Office Address

Full name of sole or fifth inventor

Sole or fifth inventor signature

Date

Residence

Citizenship

Post Office Address

Full name of sole or sixth inventor

Sole or sixth inventor signature

Date

Residence

Citizenship

Post Office Address